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NOVEL CEFEM COMPOUNDS

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NOVEL CEFEM COMPOUNDS

[Shinki Sefaimu kagobutsu]

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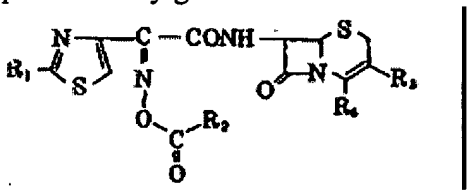
Claims

1. Cefem compounds represented by general formula



[in the formula, R1 represents an amino group or protected amino group, R2 represents a lower C1-C4 alkyl group, R3 represents a vinyl group, lower alkylthio group, -CH=CHCOOR3' (R3' is hydrogen or a lower alkyl group) or $-CH_2COO$ R3" (R3" is hydrogen or a lower alkyl group) and R4 represents a carboxyl group or protected carboxyl group] and pharmaceutically acceptable salts thereof.

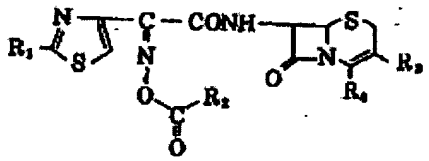
2. Syn isomers of the compounds described in Claim 1.

Detailed explanation of the invention

This invention pertains to novel cefem compounds and pharmaceutically acceptable salts thereof.

Many cephalosporin compounds are marketed and applied in clinical treatments currently, but only a few of them, including cephalexin, cefatrizine, cefaclor and cephalexin are orally administered drugs. In this regard, the present inventors conducted an investigation aiming at searching for cephalosprin compounds having a broad antibacterial spectrum and effective against resistant bacteria as well as being able to be administered orally and discovered cephalosporins having various substituents at the 7 and 3 positions of the nucleus and that certain cefem compounds had a broad antibacterial spectrum and excellent antibacterial effect when administered orally, thus accomplishing the present invention.

Specifically, the present invention pertains to novel cefem compounds having excellent antibacterial activity, and more specifically, it provides cefem compounds having general formula (I)

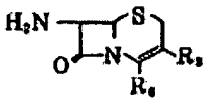


(I)

[in the formula, R1 represents an amino group or protected amino group, R2 represents a lower C1-C4 alkyl group, R3 represents a vinyl group, lower alkylthio group, -CH=CHCOOR3' (R3' is hydrogen or a lower alkyl group) or $-CH^2COO$ R3" (R3" is hydrogen or a lower alkyl group) and R4 represents a carboxyl group or protected carboxyl group] and pharmaceutically acceptable salts thereof /2*

Compounds (I) of the present invention can be synthesized by any of the following methods.

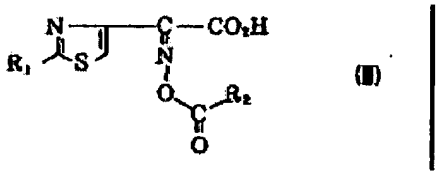
① Synthesizing compounds (I) of the present invention by reacting compounds represented by general formula (II)



(II)

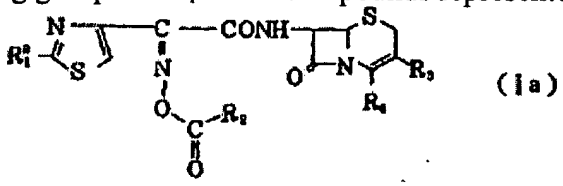
(in the formula, R3 and R4 are the same as the aforementioned)
or N-silyl compounds thereof with compounds represented by general formula (III)

* [Numbers in the right margin represent pagination in the foreign text.]

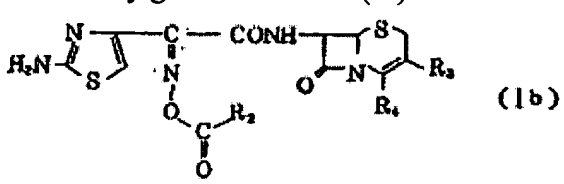


(in the formula, R1 and R2 are the same as the aforementioned)
or carboxyl group thereof, followed by removing the protecting groups if necessary.

② Removing the protecting groups of R_1^a from compounds represented by general formula (Ia)

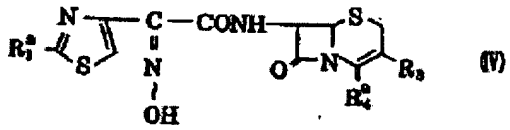


(in the formula, R_1^a represents protected amino groups while R2, R3 and R4 are the same as the aforementioned)
to produce compounds represented by general formula (Ib)



(in the formula, R2, R3 and R4 are the same as the aforementioned)

③ Synthesizing compounds (I) of the present invention by reacting compounds represented by general formula (IV)



(in the formula, R_4^a represents protected carboxyl groups, and R_1^a and R3 are the same as the aforementioned)
with compounds represented by general formula (V) or (VI)

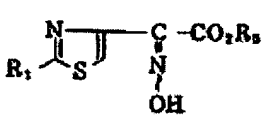
$$R_2COX \quad (V) \qquad R_2COCH_2X \quad (VI)$$

(in the formula, X represents halogen atoms, and R2 is the same as the aforementioned)

In the aforementioned formulas (I)-(VI), "lower" means 1-4 carbons unless otherwise specified. The protecting groups for the amino group represented by R_1^a may be any conventional group as long as it can be detached when desired and the preferably applicable examples include 2,2,2-trichloroethoxycarbonyl group, 2-methylsulfonylethyloxycarbonyl group, 1-butoxycarbonyl group, chloroacetyl group and trityl group. The protecting groups for the

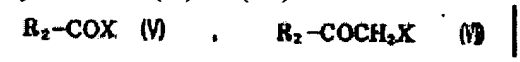
carboxyl group represented by R_4^a may be any conventional group utilized for β-lactam compounds and the examples include diphenylmethyl group, p-nitrobenzyl group, trichloroethyl group, p-methoxybenzyl group and aryl group. Also, examples of the reactive derivatives of the carboxyl groups of compounds (III) include acid halide compounds, acid azides, acid anhydrides, mixed acid anhydrides, active amides and active esters. Also, chlorine, bromine and iodine can be cited as the halogen atoms of compounds (V) and (VI).

Compounds represented by formula (III) as the starting materials in method ① of the present invention can be produced, for example, by reacting compounds represented by general formula (VII)



(in the formula, R5 represents a carboxyl protecting group, and R1 is the same as the aforementioned)

with compounds represented by formula (V) or (VI)



(in the formula, R2 and X are the same as the aforementioned), followed by removing the carboxyl protecting groups.

The reaction with compound (V) or compound (VI) is conducted in an organic solvent, water or a solvent containing water in the presence of an alkali. Removal of the carboxyl protecting group must be conducted under a condition that does not cause the cleavage of the acyl group of the oxime or the decomposition of oxyimino group. For this reason, the method of removal with palladium catalyst using an allyl group (J. Org. Chem., 47-587, 1982), or the method of acid hydrolysis using the t-butyl group, p-methoxybenzyl group or diphenylmethyl group as R5 is applied.

In method ① of the present invention, if a reactive derivative of the carboxyl group of compounds represented by formula (III) is utilized, the reaction is preferably conducted on an ice bath in a solvent that is not adversely affecting the reaction, for example, water, acetone, dioxane, acetonitrile, chloroform, methylene chloride, tetrahydrofuran or ethyl acetate. Also, if compounds of formula (III) are utilized in their free forms, the reaction is preferably conducted in the presence of a condensing agent. Examples of such condensing agents include the so-called Vilsmeier reagents obtained from the reaction of N,N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinoethylcarbodiimide; N-dicyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide; N,N'-diethylcarbodiimide; N,N'-diisopropylcarbodiimide; N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide; N,N'-carbonylbis(2-methylimidazol); pentamethyleneketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine; ethoxyacetylene;

1-alkoxy-1-chloroethylenes; trialkyl phosphites; ethyl polyphosphate; isopropyl polyphosphate; phosphorus oxychloride; phosphorus trichloride; thionyl chloride; oxaly chloride; triphenyl phosphine; 2-ethyl-7-hydroxybenzisooxazolium chloride; 2-ethyl-5-(m-sulfophenyl)isooxazolium hydroxide intermolecular salt; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole or dimethylformamide with thionyl chloride, phosgene or phosphorus oxychloride.

This reaction can also be conducted in the presence of an inorganic alkali or organic alkali, and the examples of the alkalis include alkali metal hydrogen carbonates (for example, sodium hydrogen carbonate, potassium hydrogen carbonate), alkali carbonates (for example, sodium carbonate, potassium carbonate), alkaline-earth metal carbonates (for example, calcium carbonate, etc.), tri(lower)alkylamines (for example, trimethylamine, triethylamine, etc.), pyridine, N-(lower)alkylmorpholines and N,N'-di(lower)alkylbenzylamines, etc.

There is no particular restriction to the reaction temperature, but the reaction is in general conducted under cooling or heating.

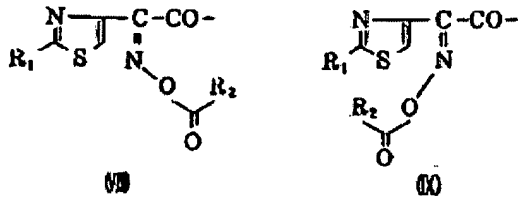
The syn isomers of the objective compounds (I) of the present invention can be obtained from the reaction of the corresponding syn isomers of compounds (II) and compounds (III) under neutral condition in the presence of the aforementioned Vilsmeier reagent, for example.

Also, the reaction of method ③ of the present invention can be conducted by conventionally known methods. Specifically, the reaction of compounds (IV) and (V) can be conducted at -20–20°C in a solvent such as methylene chloride, ethyl acetate or tetrahydrofuran in the presence of an organic alkali such as pyridine or triethylamine or an inorganic alkali such as potassium carbonate or sodium bicarbonate. Also, the reaction of compounds (IV) and (VI) is preferably conducted at 0–5°C in a solvent such as dimethylformamide or dimethyl sulfoxide.

Furthermore, the removal of the protecting groups in methods ①–③ of the present invention can be conducted by conventional methods in response to the type, and methods such as acid hydrolysis, alkali hydrolysis and reduction can be applied, for example.

Syn isomers and anti isomers are present in compounds (I), (Ia) and (Ib) of the present invention and in starting materials (III), (IV) and (VII), and the two types of isomers and any mixture thereof are all included in the present invention. /4

In this regard, the syn isomers and anti isomers of the objective compounds (I) mean geographic isomers having the following partial structures (VIII) and (IX), respectively.



(in the formulas, R1 and R2 are the same as the aforementioned)

In case the compounds of the present invention contain free carboxyl groups and/or free amino groups, pharmaceutically acceptable salts thereof can be derived by conventional methods. Said salts are the normal, nontoxic salts, and examples of such salts include metal salts such as alkali metal salts (for example, sodium salts, potassium salts, etc.) and alkaline-earth metal salts (for example, calcium salts, magnesium salts, etc.), salts with organic bases (for example, trimethylamine salts, triethylamine salts, pyridine salts, picoline salts, dicyclohexylamine salts, N,N'-dibenzylethylenediamine salts, etc.), salts with organic acids (for example, acetates, maleates, succinates, methane sulfonates, benzene sulfonates, formates, toluene sulfonates, etc.), salts with inorganic acids (for example, hydrochlorides, hydrobromides, sulfates, phosphates, etc.) and salts with amino acids (for example, alginates, asparaginates, glutaminates, etc.).

The objective compounds (I) and pharmaceutically acceptable salts thereof of the present invention are novel compounds showing potent antibacterial activity, which inhibit the growth of a wide range of pathogenic microorganisms including gram-positive bacteria and gram-negative bacteria, and are particularly useful as antibacterial agents for oral administration. When the objective compounds (I) and pharmaceutically acceptable compounds thereof of the present invention are utilized for therapeutic purpose, the aforementioned compounds are incorporated as active ingredients, which are administered in conventional drug forms by blending with pharmaceutically acceptable carriers. Examples of the carriers include organic and inorganic, solid and liquid excipients suitable for oral administration, nonoral administration and external application. Also, the drug forms include capsules, tablets, sugar-coated tablets, ointments, suppositories, solutions, suspensions and emulsions.

The result of the antibacterial activities investigated for the representative compounds of the present invention are shown in the following for the purpose of showing the usefulness of the objective compounds provide by the present invention.

1. Antibacterial activity

(a) Test method

The test was conducted by the dilution method with agar plate, and the minimum inhibitory concentrations (MIC) for inhibiting the growth of bacteria shown in Table 1 were recorded. Table 1 shows the results.

(b) Test compounds

A: 7-[2-(2-aminothiazol-4-yl)-2-acetyloxyiminoacetamido]-3-methylthio-3-cefem-4-carboxylic acid trifluoroacetic acid salt (syn isomer)

B: 7-[2-(2-aminothiazol-4-yl)-2-pivaloyloxyiminoacetamido]-3-methylthio-3-cefem-4-carboxylic acid trifluoroacetic acid salt (syn isomer)

C: 7-[2-(2-aminothiazol-4-yl)-2-propionoyloxyiminoacetamido]-3-methylthio-3-cefem-4-carboxylic acid trifluoroacetic acid salt (syn isomer)

D: 7-[2-(2-aminothiazol-4-yl)-2-isobutyryloxyiminoacetamido]-3-methylthio-3-cefem-4-carboxylic acid trifluoroacetic acid salt (syn isomer)

E: 7-[2-(2-aminothiazol-4-yl)-2-pivaloyloxyiminoacetamido]-3-ethylthio-3-cefem-4-carboxylic acid trifluoroacetic acid salt (syn isomer)

F: 7-[2-(2-aminothiazol-4-yl)-2-pivaloyloxyiminoacetamido]-3-methoxycarbonylmethyl-3-cefem-4-carboxylic acid sodium salt (syn isomer) /5

G: 7-[2-(2-aminothiazol-4-yl)-2-pivaloyloxyiminoacetamido]-3-vinyl-3-cefem-4-carboxylic acid trifluoroacetic acid salt (syn isomer)

① 試験菌	② 試験化合物						
	A	B	C	D	E	F	G
Sta. aureus 606	0.78	1.56	0.78	0.78	25	6.25	1.56
Sta. aureus 606 E 25	0.78	1.56	0.78	0.78	25	3.13	1.56
Sta. aureus 209P JC-1	0.20	0.39	0.20	0.39	6.25	1.56	0.39
Sta. aureus Smith (I)	0.20	0.78	0.20	0.39	12.5	1.56	0.78
Sta. epidermidis ATCC 14990	0.20	0.78	0.20	0.37	6.25	1.56	0.78
B. subilis ATCC 6633	0.39	0.78	0.39	0.39	12.5	3.13	0.78
E. coli W3630 RGN823	0.78	6.25	0.78	1.56	12.5	12.5	6.25
E. coli W3630 RGN14	0.78	12.5	1.56	3.13	12.5	25	6.25
E. coli W3630 RGN238	1.56	6.25	1.56	1.56	12.5	25	6.25
E. coli ML1410	0.78	12.5	1.56	3.13	12.5	25	12.5
E. clli NIHJ JC-2	0.78	3.13	0.78	1.56	12.5	12.5	6.25
E. coli No.29	0.39	3.13	0.78	0.78	12.5	6.25	3.13
Kleb. pneumoniae GN69	0.39	1.56	0.39	0.78	6.25	6.25	1.56
Kleb. pneumoniae GN118	0.39	3.13	0.39	0.78	6.25	12.5	3.13
Kleb. pneumoniae PCI602	0.78	3.13	0.39	0.78	6.25	12.5	3.13
Pro. mirabilis GN79	1.56	6.25	25	3.13	25	25	3.13
Pro. mirabilis GN310						12.5	25
Sal. typhi O-901-W	0.39	0.78	0.20	0.39	6.25	6.25	0.78

① 試験菌	② 試験化合物						
	A	B	C	D	E	F	G
Sal. typhimurium LT-2	0.39	3.13	0.39	0.78	12.5	12.5	1.56
Sal. enteritidis No.11	0.20	0.20	0.10	0.10	6.25	0.78	0.20
Shigella dysenteriae Shigae	0.20	0.78	0.20	0.39	6.25	3.13	0.78
Pro. vulgaris GN76	1.56	6.25	6.25	12.5	50	12.5	3.13
Pro. vulgaris GN106	0.78	3.13	1.56	3.13	50	12.5	3.13
Pro. vulgaris OX-19						12.5	12.5
Pro. morganii Köno						25	50
Pro. rettgeri GN624	0.20	1.56	0.39	0.78	6.25	3.13	3.13
Pro. rettgeri J-0026	0.20	0.78	0.20	0.39	6.25	1.56	1.56
E. coli GN206						6.25	6.25
Citro. freundii GN346/16	1.51	6.25	0.78	1.56	12.5	25	6.25
Entero. cloacae G-0005						50	12.5
Entero. cloacae G-0008			6.25	6.25	25	25	6.25
Serr. marcescens No.1	1.51	6.25	3.13	3.13	25	25	6.25
Serr. marcescens No.2	3.13		3.13	3.13	25	50	12.5
Ps. cepacia M-0527	1.56	12.5	3.13	3.13	12.5	12.5	12.5
Str. faecalis W-75					12.5		

Key: 1 Tested bacteria
2 Tested compounds

2. Therapeutic experiment of infection /6

(a) Test method

ICR-JCL mice (4-week-old males, weight 20 ± 0.5 g), 3 mice/group, were utilized as the test animals. The bacterium for infection was *Escherichra coli* No. 29, which was incubated at 37°C for 20 h in heart infusion agar and suspended in physiological saline solution, followed by mixing muein to give a concentration of 2.5 % and injecting into the abdomens of the mice. Drug samples were orally administered at various concentrations immediately after the bacterial infection, and the number of surviving mice was counted after 7 days. Table 2 shows the result.

(b) Compounds tested

H: 7-[2-(2-aminothiazol-4-yl)-2-acetyloxyiminoacetamido]-3-methylthio-3-cefem-4-carboxylic acid pivaloyloxymethyl ester (syn isomer)

I: 7-[2-(2-aminothiazol-4-yl)-2-pivaloyloxyiminoacetamido]-3-methylthio-3-cefem-4-carboxylic acid pivaloyloxymethyl ester (syn isomer)

① 投与量 (mg/マウス)	② 生存率 A*	B*	E*	H	I	セフロキサジン ③	無治療対照群 ④
10	3/3	3/3	3/3	3/3	3/3	3/3	0/3
1	3/3	3/3	3/3	3/3	3/3	2/3	0/3
0.1	0/3	2/3	2/3	2/3	2/3	0/3	0/3

⑤ * 試験化合物A、B及びEは前記と同じ。

Key: 1 Dosage (mg/mouse)
2 Survival rate
3 Cefloxacin
4 Untreated control group
5 Test compounds A, B and E are the same as the aforementioned.

Next, the present invention is explained in detail using reference examples and application examples, but they are not to be construed as limiting the present invention.

Reference Example 1

Ethyl 2-(2-aminothiazol-4-yl)-2-hydroxyiminoacetate (syn isomer): /7

A solution of 30 g of ethyl acetoacetate in 30 mL of glacial acetic acid was chilled on ice while stirring, to which a solution of 18 g of sodium nitrite in 40 mL of water was added at a rate

such that the reaction temperature was maintained at below 10°C. After stirring for about 30 min on ice, 16 g of potassium chloride in 80 mL of water was added. The resultant mixture was stirred for 1 h. The lower organic layer was separated and the aqueous layer was extracted with diethyl ether. The extract was combined with the oily layer, which was washed sequentially with water and saturated aqueous table salt solution, followed by concentrating until dry to give 30 g of ethyl-2-hydroxyimino-3-oxobutyrate (syn isomer). A solution of 1.5 g of ethyl 2-hydroxyimino-3-oxobutyrate (syn isomer) in 40 mL of methylene chloride was stirring while chilling on ice, to which 14 g of sulfuryl chloride was added drop-wise, followed by stirring for 2 days. The mixture was washed with water, dried and concentrated. The residual oily substance (17 g) was dissolved in 50 mL of ethanol, to which 7.7 mL of dimethylaniline and 4.2 g of thiourea were added while stirring. The product was filtered after 2 h and washed with ethanol, followed by drying, and 7 g of the subject compound was obtained.

Mp 188°C (decomposition)

Reference Example 2

Ethyl 2-(2-tritylaminothiazol-4-yl)-2-hydroxyiminoacetate hydrochloride (syn isomer):

A solution 8.4 mL of triethylamine and 13 g of the product of Reference Example 1 in 30 mL of dimethylformamide was stirred and chilled (-30°C), and 16.75 g of trityl chloride was added to the mixture over 2 h. The mixture was stirred for 30 min at the same temperature and for 17 h at room temperature.

Next, it was partitioned in 500 mL of water and 500 mL of ethyl acetate. The organic layer was separated and washed with water and then stirred in 500 mL of 1N HCl. The precipitates were collected and washed sequentially with water, ethyl acetate and ether, followed by drying, and 16.4 g of the subject compound was obtained as white solids.

Mp 184-186°C (decomposition)

Reference Example 3

2-(2-tritylaminothiazol-4-yl)-2-hydroxyiminoacetic acid sodium salt (syn isomer):

20 g of ethyl 2-(2-tritylaminothiazol-4-yl)-2-hydroxyiminoacetate hydrochloride (syn isomer) was suspended in 400 mL of ethanol, and 400 mL of a 1N aqueous NaOH solution was added drop-wise. After stirring for 24 h at room temperature, the precipitates were filtered. The precipitates were washed with ether and then suspended in 500 mL tetrahydrofuran and the pH was adjusted to 2.0 with 10% HCl while chilling on ice to give a homogeneous solution. Next, the pH was adjusted to 8.0 with saturated aqueous sodium bicarbonate, and precipitates were formed. The precipitates were filtered and washed sequentially with water and ether, followed by drying, and 16 g of white powder was obtained.

Reference Example 4

2-(2-tritylaminothiazol-4-yl)-2-hydroxyiminoacetic acid allyl ester (syn isomer):

1.8 g of 2-(2-tritylaminothiazol-4-yl)-2-hydroxyiminoacetic acid sodium salt was dissolved in 20 mL of dimethylformamide, to which 0.8 mL of allyl iodide was added while chilling on ice, and the mixture was stirred for 24 h at room temperature. The reaction solution was added to a mixture of 200 mL of ethyl acetate and 200 mL of water, and the organic layer was washed with water (200 mL x 2). After drying over magnesium sulfate and concentrating, the product was purified with 60 g of Wako gel C-200 (system: toluene-ethyl acetate). Amount yielded: 1.3 g.

NMR (80 MHz, δ value, PPM, $CDCl_3$):

4.85 (2H, m), 5.25-5.50 (2H, m), 5.95 (1H, m), 6.90 (1H, s), 7.85 (16H, b.s)

Reference Example 5

2-(2-tritylaminothiazol-4-yl)-2-acetyloxyiminoacetic acid allyl ester (syn isomer):

469 mg of 2-(2-tritylaminothiazol-4-yl)-2-hydroxyiminoacetic acid allyl ester (syn isomer) was dissolved in 10 mL of dry methylene chloride, to which 0.1 mL of pyridine was added while chilling on ice. Next, 1 mL of dry methylene chloride containing 0.1 mL of acetyl chloride was added drop-wise, followed by stirring for 20 min at the same temperature. The solution was washed with water and dried over magnesium sulfate. After concentrating, the residue was purified with silica gel and 500 mg of the objective product was obtained. /8

FD mass: 511

IR (Nujol): 3300, 1740 cm^{-1}

NMR (80 MHz, δ value, PPM):

2.11 (3H, s), 4.75-4.85 (2H, m), 5.20-5.48 (2H, m), 5.70-6.15 (1H, m), 6.85 (1H, s), 7.80 (15H, s)

The compounds of the following Reference Examples 6-8 were obtained in the same manner as in Reference Example 5 by reacting 2-(2-tritylaminothiazol-4-yl)-2-hydroxyiminoacetic acid allyl ester (syn isomer) with corresponding acid chlorides.

Reference Example 6

2-(2-tritylaminothiazol-4-yl)-2-propionoyloxyiminoacetic acid allyl ester (syn isomer):

FD mass: 525

IR (Nujol): 3300, 1740 cm^{-1}

NMR (80 MHz, δ value, PPM):

1.25 (3H, t, J = 8 Hz), 2.5 (2H, q, J = 8 Hz), 4.75-4.85 (2H, m), 5.20-5.48 (2H, m), 5.70-6.15 (1H, m), 6.82 (1H, s), 7.80 (15H, b,s)

Reference Example 7

2-(2-tritylaminothiazol-4-yl)-2-isobutyryloxyiminoacetic acid allyl ester (syn isomer):

FD mass: 540

IR (Nujol): 3300, 1745 cm^{-1}

NMR (80 MHz, δ value, PPM):

1.20 (6H, d, J = 8 Hz), 2.60 (1H, m), 4.70-4.82 (2H, m), 5.15-5.48 (2H, m), 5.70-6.15 (1H, m), 6.85 (1H, s), 7.20 (16H, s)

Reference Example 8

2-(2-tritylaminothiazol-4-yl)-2-pivaloyloxyiminoacetic acid allyl ester (syn isomer):

FD mass: 553

IR (Nujol): 3300, 1740 cm^{-1}

NMR (80 MHz, δ value, PPM):

1.25 (9H, s), 4.70-4.85 (2H, m), 5.16-5.55 (2H, m), 5.65-6.20 (1H, m), 6.90 (1H, s), 7.26 (16H, s)

Reference Example 9

2-(2-tritylaminothiazol-4-yl)-2-acetyloxyiminoacetic acid (syn isomer):

250 mg of 2-(2-tritylaminothiazol-4-yl)-2-acetyloxyiminoacetic acid allyl ester (syn isomer) was dissolved in 10 mL of dry methylene chloride, to which 5 mL of a solution of 85 mg potassium 2-ethylhexanoate in ethyl acetate was added while chilling on ice, followed by adding 12 mg of triphenyl phosphine and 12 mg of tetrakistriphenylphosphine palladium (0), and the mixture was stirred for 1 h at the same temperature. The precipitates were filtered and washed sequentially with isopropyl ether and ethyl acetate, followed by drying, and potassium 2-(2-tritylaminothiazol-4-yl)-2-acetyloxyiminoacetate was obtained. The potassium salt obtained was then suspended in 20 mL ethyl acetate and the pH was adjusted to 2.0 with 5% HCl while chilling on ice. The product was washed with saturated aqueous table salt solution and dried, and 130 mg of the objective compound was obtained as white powder after concentrating and drying.

NMR (80 MHz, δ value):

2.15 (3H, s), 6.80 (1H, s), 7.30 (16H, b,s)

The compounds of the following Reference Examples 10-12 were obtained in the same manner as in Reference Example 9 by using corresponding

2-(2-tritylaminothiazol-4-yl)-2-alkylacyloxyiminoacetic acid allyl esters (syn isomer) as the starting materials and reacting with potassium 2-ethylhexanoate in the presence of a palladium catalyst.

Reference Example 10

2-(2-tritylaminothiazol-4-yl)-2-propionoyloxyiminoacetic acid (syn isomer):

NMR (80 MHz, δ value, PPM, $CDCl_3$):

1.25 (3H, t, J = 8 Hz), 2.5 (2H, q, J = 8 Hz), 6.80 (1H, s), 7.30 (16H, b.s)

Reference Example 11 /9

2-(2-tritylaminothiazol-4-yl)-2-isobutyryloxyiminoacetic acid (syn isomer):

NMR (80 MHz, δ value, PPM, $CDCl_3$):

1.05 (6H, d, J = 8 Hz), 2.40 (1H, m), 6.85 (1H, s), 7.30 (16H, b.s)

Reference Example 12

2-(2-tritylaminothiazol-4-yl)-2-pivaloyloxyiminoacetic acid (syn isomer):

NMR (80 MHz, δ value, PPM, $CDCl_3$):

1.16 (9H, s), 6.80 (1H, s), 7.28 (16H, b.s)

Reference Example 13

7-β-phenylacetamido-3-methylthio-3-cefem-4-carboxylic acid p-nitrobenzyl ester:

5.6 g (12 mM) of 7-β-phenylacetamido-3-hydroxy-3-cefem-4-carboxylic acid-p-nitrobenzyl ester was suspended in 40 mL of dry acetonitrile, which was chilled at -20°C while being stirred in nitrogen atmosphere, and 2.4 mL of diisopropylethylamine and 2.8 mL of diphenyl chlorophosphate were added. The reaction mixture was stirred for about 30 min at the same temperature, and a transparent solution was obtained. Completion of the reaction was verified by TLC and the reaction solution was chilled at -30°C, and 2.4 mL of diisopropylethylamine was added, followed by blowing in about 3 g of methyl mercaptan. Reaction was continued for about 2 h at -25 – -30°C (precipitation of crystals), and after completion of the reaction was verified with TLC, 0.5 mL of acetic acid was added.

The resultant product was collected and washed sequentially with 7 mL of cold acetonitrile and 10 mL of isopropyl ether, followed by vacuum drying. Amount yielded: 4.95 g (yield: 83%).

Mp: 231°C (decomposition)

IR: (Nujol): 3230, 1775 (β-lactam), 1705 and 1650 cm^{-1}

UV λmax: 319 nm

NMR (DMSO-d6 + $CDCl_3$): δ value (60 MHz)

3.28 (3H, s), 3.61 (2H, s), 3.68 (2H, s), 5.03 (1H, d, (J=4.6 Hz)), 5.73 (2H, s), 5.64 (1H, dd, (J=4.6, J=7.8 Hz)), 7.29 (5H, s), 7.63, 8.20 (4H, 2xd, (J=8.2))), 8.83 (1H, d, (J=7.8)

Reference Example 14

7-Phenylacetamido-3-methylthio-3-cefem-4-carboxylic acid:

2.5 g of 7-phenylacetamido-3-methylthio-3-cefem-4-carboxylic acid p-nitrobenzyl ester [mp. 231°C (decomposition)] was added to 15 mL of dioxane and 10 mL of 85% formic acid, followed by heating at 50-55°C, and 1.5-3 g of zinc powder was added in a few increments while stirring, and the reaction was further conducted for 2-5 h. Completion of the reaction was verified by thin layer chromatography (TLC) and the reaction mixture was chilled to room temperature, and the insoluble substance was collected and washed with dioxane. The reaction solution and the washing solution were combined and the majority of the solvent was removed by vacuum distillation. 10 mL of ethyl acetate and 50 mL ice water were mixed and stirred, and the pH was adjusted to 7.0-7.5 with an acidic solution of sodium carbonate, to which the above reaction solution was added drop-wise. After completing the addition, the insoluble substance was collected and washed with water. The aqueous layer and the washing solution were combined and extracted several times with ethyl acetate. The organic layer was washed with a small amount of water, and the washing solution was combined with the aqueous layer. Treatment with activated carbon is conducted if necessary. The pH of the aqueous layer was adjusted to 1-2 with hydrochloric acid, followed by standing overnight. The solid substance was collected and washed with water, followed by washing with a small amount of isopropyl ether and drying, and the subject compound was obtained. Amount yielded: 1.4 g (yield: 77%). The product was recrystallized from acetone + isopropyl ether.

Mp: 197-98°C (decomposition)

UV λmax: 318 nm (95% ethanol)

IR: (Nujol): 3280 (NH), 1770 (β-lactam), 1690 and 1640 cm^{-1}

NMR (DMSO-d6 + $CDCl_3$): δ value [60 MHz (R600)]

2.33 (3H, s), 3.57 (2H, s), 3.67 (2H, s), 5.01 (1H, d, J=4.7 Hz), 5.56 (1H, dd, J=4.7, J=8.2 Hz), 7.25 (5H, s), 9.01 (1H, d, J=8.2 Hz)

Reference Example 15

7-Phenylacetamido-3-methylthio-3-cefem-4-carboxylic acid diphenylmethyl ester:

1.82 g of 7-phenylacetamido-3-methylthio-3-cefem-4-carboxylic acid obtained in /10
Reference Example 14 was heated and dissolved in acetone. A solution of diazodiphenylmethane in n-hexane was added. The mixture was reacted overnight at room temperature while the

progress of the reaction was traced by TLC, and the solution was concentrated under vacuum to remove the solvent. The excess diazodiphenylmethane was removed by treating with n-hexane. The solid substance was dissolved in methylene chloride and the pH was adjusted to 7.5 with aqueous acidic sodium carbonate solution. The methylene chloride layer was separated, dried and concentrated under vacuum to remove the solvent, and the solid substance was treated with isopropyl ether and ethyl ether, followed by drying to obtain the subject compound. Amount yielded: 2.4 g (90%). The product was recrystallized from acetone + methanol.

Mp: 162-63°C (decomposition)

UV λmax: 318 nm (95% ethanol)

IR: (Nujol): 3230 (NH), 1780 (β-lactam), 1700 (ester) and 1650 cm^{-1}

NMR ($CDCl_3$): δ value (60 MHz)

1.99 (3H, s), 2.91, 3.38 (2H, ABq, J=16.8 Hz), 3.64 (2H, s), 4.95 (1H, d, J=4.3 Hz), 5.62 (1H, d.d, J=4.3, J=8.6 Hz), 6.86 (1H, s), 7.2-7.33 (16H)

Reference Example 16

7-Amido-3-methylthio-3-cefem-4-carboxylic acid diphenylmethyl ester hydrochloride:

2.65 g of 7-phenylacetamido-3-methylthio-3-cefem-4-carboxylic acid diphenylmethyl ester obtained in Reference Example 15 was dissolved in 50 mL of methylene chloride, followed by chilling to -30°C and 4 mL of anhydrous pyridine was added to this solution and 3.2 g of phosphorus pentachloride was further added as a micropowder. The temperature was gradually increased and the mixture was stirred for about 3 h at -10 −10°C. The solution was chilled to -40°C after the completion of the reaction was verified with TLC. (A part of the reaction solution was taken and methanol was added to it, followed by developing with benzene:ethyl acetate = 2:1). 15 mL of anhydrous methanol was added drop-wise to the reaction solution (crystals precipitated) under agitation. The temperature of the transparent solution was gradually increased and the solution was stirred for about 1 h at -10°C. The solution was added to 40 mL of cold aqueous table salt solution after the completion of the reaction was verified with TLC, and while stirring, dilute ammonia water was added to maintain the pH at 1.5-2.0 and reaction was carried out for about 1 h while chilling on ice. The precipitates were collected and washed sequentially with a small amount of ice water, ethyl acetate and isopropyl ether, and the subject compound was obtained after drying. Amount yielded: 22.5 g (91%).

Mp: 203-205°C (decomposition)

UV λmax: 319 nm (95% ethanol)

IR: (Nujol): 1780 (β-lactam), 1760 and 1700 cm^{-1}

NMR (DMSO-d_6): δ value (60 MHz)

2.44 (3H, s), 3.73, 4.13 (2H, ABq, J=16 Hz), 5.08 (1H, d, J=4.3 Hz), 5.28 (1H, d, J=4.3 Hz), 6.90 (1H, s), 7.20-7.80 (13H, m)

Reference Example 17

7-Amino-3-ethylthio-3-cefem-4-carboxylic acid benzhydryl ester hydrochloride:

The subject compound was obtained in accordance with Reference Examples 13-16.

Mp: 172-173°C (decomposition)

UV λmax: 319 nm (95% ethanol)

IR: (Nujol): 1778, 1705 cm^{-1}

NMR (DMSO-d_6): δ value (60 MHz)

1.16 (3H, t, J=7 Hz), 2.93 (2H, q, J=7 Hz), 2.93 (2H, q, J=7 Hz), 3.68, 4.10 (2H, ABq, J=15 Hz), 5.05 (1H, d, J=5 Hz), 5.77 (1H, d, J=5 Hz), 6.83 (1H, s), 7.30 (10H, m)

Reference Example 18

7-Phenylacetamido-3-vinyl-3-cefem-4-carboxylic acid diphenylmethyl ester:

1.2 g of 7-phenylacetamido-3-bromomethyl-3-cefem-4-carboxylic acid diphenylmethyl ester was dissolved in 2 mL of dimethylformamide, to which 818 mg of triphenyl phosphine and 311 mg of sodium iodide were added, and the mixture was stirred at 0-5°C for 17 h. The reaction solution was treated with isopropyl ether and powder was obtained, which was further washed with ethyl acetate. The resultant powder was suspended in 30 mL of methylene chloride and 15 mL of 36% formaldehyde was added while chilling on ice. The pH was then adjusted to 9.0 with a saturated aqueous solution of sodium bicarbonate, followed by stirring for 30 min on an ice bath and for 2 h at room temperature. The pH was then adjusted to 5.0 with 5% HCl while chilling on ice, and the solution was extracted with methylene chloride and the extract was washed with water and dried over magnesium sulfate. The solution was concentrated and the residue was subjected to purification by silica gel chromatography (Wako gel C-200, 40 g, system: toluene-ethyl acetate), and 420 g of the objective product was obtained. /11

IR: (Nujol): 1765, 1710 cm^{-1}

NMR (80 MHz, δ value, PPM, $CDCl_3$)

3.30, 3.60 (2H, ABq, J=19 Hz), 3.56 (2H, s), 4.91 (2H, d, J=4.8 Hz) 5.16 (1H, d, J=8 Hz), 5.36 (1H, d, J=15 Hz), 5.75 (1H, d,d, J=4.8, 9.0 Hz), 6.25 (1H, d, J=9.0 Hz), 6.89 (1H, s), 7.10-7.55 (16H, m)

Reference Example 19

7-Amino-3-vinyl-3-cefem-4-carboxylic acid diphenylmethyl ester hydrochloride:

230 g of 7-phenylacetamido-3-vinyl-3-cefem-4-carboxylic acid benzhydryl ester was dissolved in 10 mL of dry methylene chloride, which was chilled at -40°C. 0.36 mL of pyridine and 282 mg of phosphorus pentachloride were added to the mixture, which was stirred at -40°C for 2 h and at 0°C for 2 h. Afterward, the solution was chilled at -50°C and 1 mL of dry methanol was added, which was stirred at -50°C for 2 h and at 0°C for 1 h. 10 mL of saturated aqueous table salt solution was added to the reaction solution while chilling on ice, followed by stirring at 0°C-5°C for 30 min. 20 mL of isopropyl ether was added to the solution and the precipitates were filtered, which was washed sequentially with isopropyl ether and ethyl acetate, and 164 mg of the objective product was obtained.

IR: (Nujol): 1760, 1705 cm^{-1}

NMR (60 MHz, δ value, PPM, DMSO-d_6)

3.73, 4.00 (2H, ABq, J=18 Hz), 5.1-5.4 (2H, m), 5.58 (1H, d, J=6 Hz), 5.93 (1H, m), 6.97 (1H, s), 7.00 (1H, d.d, J=12, 18 Hz), 7.42 (10H, m), 9.17 (2H, m)

Reference Example 20

7-Amino-3-methylthio-3-cefem-4-carboxylic acid ethoxycarbonyloxyethyl ester hydrochloride (α form):

481 mg (0.001 mol) of 7-phenylacetamido-3-methylthio-3-cefem-4-carboxylic acid ethoxycarbonyloxyethyl ester (α form) (mp 157-58°C) was dissolved in 20 mL of dry methylene chloride, to which 0.40 mL of pyridine was added, followed by chilling at -20°C. 440 mg of phosphorus pentachloride was added to it and reaction was conducted for about 90 min by gradually increasing the temperature to +5 – +10°C (reacted for 30 min after phosphorus pentachloride disappeared). The reaction solution was chilled at -30°C and a solution containing 2 mL of isobutanol and 5 mL of methylene chloride was added drop-wise while stirring. The temperature was increased gradually to +5 – +10°C and reaction was conducted for 2 h (the reaction was traced with TLC). The temperature was decreased to 0°C after the reaction was complete and 5 mL of cold water containing 2 mL of aqueous table salt solution was poured into the solution. The mixture was stirred for about 60 min while being chilled on ice, and 10 mL of diisopropyl ether and 10 mL of ethyl ether were added. After a short while, white crystals precipitated out gradually. The crystals were collected, which was washed with diisopropyl ether and ether, followed by drying. Amount yielded: 360 mg.

mp 148-50°C (decomposition)

UV λmax: 321 nm (95% ethanol)

IR: (Nujol): 1781, 1762, 1700 cm^{-1}

Reference Example 21

7-Amino-3-ethylthio-3-cefem-4-carboxylic acid ethoxycarbonyloxyethyl ester hydrochloride:

The same reaction as in Reference Example 20 was conducted using 990 mg (0.002 mol) of 7-phenylacetamido-3-ethylthio-3-cefem-4-carboxylic acid ethoxycarbonyloxyethyl ester (mp 130-31°C). 750 mg (90.8%) of the subject compound was obtained.

mp 188-90°C (decomposition)

UV λmax: 320 nm (95% ethanol)

IR: (Nujol): 1780, 1763, 1710 cm^{-1}

Reference Example 22

7-Phenylacetamido-3-methoxycarbonylmethyl-3-cefem-4-carboxylic acid p-nitrobenzyl ester:

4.7 g of 7-phenylacetamido-3-hydroxy-3-cefem-4-carboxylic acid p-nitrobenzyl ester was dissolved in 35 mL of dimethylformamide, to which 4 g of carbomethoxymethylene triphenyl phosphorane was added, and the mixture was stirred at room temperature for 24 h. The reaction solution was concentrated and the residue was dissolved in 500 mL of ethyl acetate, followed by /12
washing with 5% HCl, water and saturated aqueous table salt solution and drying over magnesium sulfate. The solution was concentrated and the residue was subjected to purification by column chromatography with Wako gel C-200 (200 g) (toluene-ethyl acetate system), and 28 g of the objective product was obtained.

IR: (Nujol): 3300, 1760 cm^{-1}

NMR (80 MHz, δ value, PPM, $CDCl_3$)

3.20-3.75 (9H, m), 5.00 (1H, d, J=4.8 Hz), 5.30 (2H, b.s), 5.85 (1H, d.d, J=4.8 Hz, 9 Hz), 6.15 (1H, d, J=9 Hz), 7.35 (5H, s), 7.55, 8.22 (4H, ABq, J=9.0 Hz)

882 mg of a by-product (an isomer from dimerization of the cephalosporin nuclei) was obtained from the above reaction. A product having the same physical property was obtained when this by-product was oxidized with a peracid followed by reduction with phosphorus trichloride by conventional methods.

Reference Example 23

7-Phenylacetamido-3-methoxycarbonylmethyl-3-cefem-4-carboxylic acid diphenylmethyl ester:

2.8 g of 7-phenylacetamido-3- methoxycarbonylmethyl-3-cefem-4-carboxylic acid p-nitrobenzyl ester was dissolved in 50 mL of formic acid and 50 mL of ethanol, to which 1.8 g of zinc powder was added over 10 min while stirring. The mixture was stirred at room temperature for 1 h and at 50°C for 2 h, and the insoluble substance was filtered. The filtrate was concentrated under vacuum, followed by adding a mixed solution of 50 mL ethyl acetate and

20 mL water. The pH was adjusted to 7.0 with a saturated aqueous solution of sodium bicarbonate. The insoluble substance was removed and the aqueous layer was washed with ethyl acetate. The pH of the aqueous layer was adjusted to 2.0 with 5% HCl, followed by extracting with ethyl acetate.

A solution of diphenyldiazomethane-n-hexane was added to the organic layer and reaction was conducted at room temperature. The reaction solution was concentrated under vacuum after the starting material (carboxylic acid) disappeared, and the residue was washed with isopropyl ether to give 1.27 g of the objective product.

IR: (Nujol): 3320, 1770 cm^{-1}

NMR (80 MHz, δ value, $CDCl_3$)

3.32-3.70 (9H, m), 4.95 (1H, d, J=4.8 Hz), 5.80 (2H, d.d, J=4.8 Hz, 9.6 Hz), 6.10 (1H, d, J=9.6 Hz), 6.85 (1H, s), 7.15-7.35 (16H, m)

Reference Example 24

7-Amino-3-methoxycarbonylmethyl-3-cefem-4-carboxylic acid diphenylmethyl ester:

1.12 g of phosphorus pentachloride was dissolved in 20 mL of methylene chloride, to which 1.45 mL of pyridine was added while chilling on ice. After stirring for 30 min at the same temperature, the mixture was chilled at -50°C. Subsequently, 10 mL of methylene chloride containing 1.0 g of 7-phenylacetamido-3- methoxycarbonylmethyl-3-cefem-4-carboxylic acid diphenylmethyl ester was added, followed by stirring for 2 h at -50°C and for 2 h while chilling on ice. The solution was chilled at -50°C, and 4 mL of dry methanol was added drop-wise, followed by stirring for 1 h at 0°C. 20 mL of saturated aqueous solution of sodium bicarbonate was added while chilling on ice and stirred for 30 min at the same temperature. After extracting with methylene chloride and washing with saturated aqueous solution of table salt, the pH was adjusted to 7.0 with a saturated aqueous solution of sodium bicarbonate while chilling on ice. The solution was dried and concentrated and the residue was subjected to purification with 15 g of Wako gel C-200 (system: toluene-ethyl acetate), and 350 mg of the objective product was obtained.

IR: (Nujol): 1780 cm^{-1}

NMR (80 MHz, δ value, $CDCl_3$)

1.70 (2H, b.s), 3.36-3.65 (7H, m), 4.70 (1H, d, J=4.8 Hz), 4.96 (1H, d, J=4.8 Hz), 6.90 (1H, s), 7.20-7.40 (10H, m)

Reference Example 25

7-Phenylacetamido-3-methoxycarbonylvinyl-3-cefem-4-carboxylic acid diphenylmethyl ester:

1.2 g of 7-phenylacetamido-3-bromomethyl-3-cefem-4-carboxylic acid diphenylmethyl ester was dissolved in 2 mL of dimethylformamide, to which 818 mg of triphenylphosphine and 311 mg of sodium iodide were added and the mixture was stirred at 5°C for 20 h. The reaction solution was concentrated under vacuum and powder was obtained by treating with isopropyl ether, and the powder was further washed with ethyl acetate.

The resultant salt was dissolved in 30 mL of methylene chloride, to which 580 mg of methyl glyoxalate-1 hydrate was added, and the pH was adjusted to 9 with a saturated aqueous /13
solution of sodium bicarbonate while chilling on ice, followed by stirring for 4 h at room temperature. Subsequently, the pH was adjusted to 5.0 with a 5% aqueous solution of hydrochloric acid while chilling on ice, followed by extracting with metylene chloride. After washing with water and drying over magnesium sulfate, the solution was concentrated. The residue was subjected to purification with 20g of Wako gel C-200 (system: toluene-ethyl acetate) and 184 g of the objective product was obtained.

IR: (Nujol): 1780 cm^{-1}

NMR (80 MHz, δ value, PPM, $CDCl_3$)

3.40-3.65 (7H, m), 5.0 (1H, d, J=4.2 Hz), 6.70 (1H, d, J=12 Hz), 6.8 (1H, d.d, J=4.2 Hz, 9.6 Hz), 6.15 (1H, d, J=9.6 Hz), 6.80 (1H, s), 6.82 (1H, d, J=12 Hz), 7.20-7.40 (16H, m)

Reference Example 26

7-Amino-3-methoxycarbonylvinyl-3-cefem-4-carboxylic acid diphenylmethyl ester:

164 mg of phosphorus pentachloride was dissolved in 2 mL of methylene chloride under nitrogen atmosphere, to which 0.21 mL of pyridine was added while chilling on ice. The mixture was stirred for 30 min at the same temperature. The solution was added drop-wise to a preprepared solution of 1.5 mL of methylene chloride containing 150 mg of 7-phenylacetamido-3- methoxycarbonylvinyl-3-cefem-4-carboxylic acid diphenylmethyl ester at -50°C (about 10 min). The mixture was stirred for 30 min at -50°C and for 2 h at 0-5°C, followed by chilling at -50°C, and the reaction solution was added drop-wise to 2 mL of methanol chilled at -50°C. The solution was stirred for 30 min at -50°C and for 1 h at 0-5°C, followed by adding 3 mL of saturated aqueous table salt solution and stirring for 30 min at the same temperature. After extracting with methylene chloride and washing with saturated aqueous table salt solution, the pH was adjusted to 7.0 with a 2% aqueous solution of sodium bicarbonate in the presence of saturated aqueous table salt solution, and the solution was washed with water. The solution was then dried over magnesium sulfate and concentrated. The residue was subjected

to purification with 2 g of Wako gel C-200 (system: toluene-ethyl acetate) and 73 mg of the objective product was obtained.

IR: (Nujol): 1780 cm^{-1}

NMR (80 MHz, δ value, PPM, $CDCl_3$)

1.75 (2H, b.s), 3.40 (2H, b.s), 3.56 (3H, s), 4.7 (1H, d, J=4.2 Hz), 4.9 (1H, d, J=4.8 Hz), 5.75 (1H, d, J=12 Hz), 6.85 (1H, d, J=12 Hz), 6.90 (1H, s), 7.20-7.40 (10H, m)

Application Example 1

7-[2-(2-tritylaminothiazol-4-yl)-2-pivaloyloxyiminoacetamido]-3-vinyl-3-cefem-4-carboxylic acid diphenylmethyl ester (syn isomer)

192 mg of 2-(2-tritylaminothiazol-4-yl)-2-pivaloyloxyiminoacetic acid (syn isomer), 120 mg of 7-amino-3-vinyl-3-cefem-4-carboxylic acid diphenylmethyl ester and 50 mg of 1-hydroxybenztriazole were dissolved in 10 mL of methylene chloride, which was chilled on ice, and 1 mL of methylene chloride containing 75 mg of dicyclohexylcarbodiimide was added, followed by stirring overnight at 5°C. The solution was concentrated under vacuum and the residue was dissolved in 50 mL of ethyl acetate. The insoluble substance was removed and the solution was washed sequentially with cold 5% aqueous hydrochloric acid and saturated aqueous table salt solution. After drying over magnesium sulfate, the solution was concentrated under vacuum and the residue was subjected to purification with 8 g of Wako gel C-200 (system: toluene-ethyl acetate) and 200 mg of the objective product was obtained.

IR: (Nujol): 1770, 1740-1710 cm^{-1}

NMR (80 MHz, δ value, PPM, $CDCl_3$)

1.30 (9H, s), 3.50 (2H, b.s), 5.05 (1H, d, J=5 Hz), 5.20 (1H, d, J=8 Hz), 5.40 (1H, d, J=14.5 Hz), 5.90 (1H, d.d, J=5 Hz, J=9.5 Hz), 6.90 (2H, b.s), 6.65-7.10 (1H, m), 7.15-7.40 (26H, m)

Application Example 2

7-[2-(2-tritylaminothiazol-4-yl)-2-acetyloxyiminoacetamido]-3-vinyl-3-cefem-4-carboxylic acid diphenylmethyl ester (syn isomer)

The subject compound was obtained in the same manner as in Application Example 1 using 2-(2-tritylaminothiazol-4-yl)-2-acetyloxyiminoacetic acid as the starting material.

IR: (Nujol): 3300, 1770 cm^{-1}

NMR (80 MHz, δ value, PPM, $CDCl_3$)

2.70 (3H, s), 5.0 (1H, d, J=4.8 Hz), 5.2 (1H, d, J=10 Hz), 5.4 (1H, d, J=16 Hz), 5.8 (1H, d. d, J=4.8 Hz, J=9.0 Hz), 6.8 (1H, s), 6.90 (1H, s), 7.1-7.3 (27H, m)

Application Example 3 /14

7-[2-(2-aminothiazol-4-yl)-2-pivaloyloxyiminoacetamido]-3-vinyl-3-cefem-4-carboxylic acid trifluoroacetic acid salt (syn isomer)

200 mg of 7-[2-(2-tritylaminothiazol-4-yl)-2- pivaloyloxyiminoacetamido]-3-vinyl-3-cefem-4-carboxylic acid diphenylmethyl ester (syn isomer) was dissolved in 0.4 mL of anisole, and 4 mL of cold trifluoroacetic acid was added while chilling on ice, followed by stirring for 1 h at the same temperature. The solution was concentrated under vacuum and powder was prepared (from the precipitates) by treating with isopropyl ether, which was washed and dried, and 85 mg of the objective product was obtained.

IR: (Nujol): 1760 cm^{-1}

NMR (80 MHz, δ value, PPM, DMSO-d_6)

1.15 (9H, s), 3.50, 3.86 (2H, ABq, J=17.6 Hz), 5.16 (1H, d, J=5 Hz), 5.35 (1H, d, J=9 Hz), 5.60-5.78 (2H, m), 6.75-7.10 (1H, m), 6.95 (1H, s)

Application Example 4

7-[2-(2-tritylaminothiazol-4-yl)-2-pivaloyloxyiminoacetamido]-3-methoxycarbonylmethyl-3-cef em-4-carboxylic acid diphenylmethylester (syn isomer)

256 mg of 2-(2-tritylaminothiazol-4-yl)-2-pivaloyloxyiminoacetic acid, 181 mg of 7-amino-3- methoxycarbonylmethyl-3-cefem-4-carboxylic acid diphenylmethyl ester and 67 mg of 1-hydroxybenztriazole were dissolved in 20 mL of methylene chloride, which was chilled on ice. 1 mL of methylene chloride containing 103 mg of dicyclohexylcarbodiimide was added, followed by stirring overnight at 5°C. The solution was concentrated under vacuum and the residue was dissolved in 30 mL of ethyl acetate. The insoluble substance was removed and the solution was washed sequentially with a cold 5% aqueous solution of hydrochloric acid and saturated aqueous table salt solution and dried. The solution was then concentrated under vacuum and the residue was subjected to purification with 15 g of Wako gel C-200 (system: toluene-ethyl acetate) and 100 mg of the objective product was obtained.

IR: (Nujol): 3300, 1780 cm^{-1}

NMR (80 MHz, δ value, PPM, $CDCl_3$)

1.16 (9H, s), 3.40-3.70 (7H, m), 5.10 (1H, d, J=5 Hz), 5.8 (1H, d. d, J=5 Hz, J=9.6 Hz), 6.8 (1H, s), 6.85 (1H, s), 7.2-7.4 (26H, m)

Application Example 5

7-[2-(2-aminothiazol-4-yl)-2-pivaloyloxyiminoacetamido]-3-methoxycarbonylmethyl-3-cefem-4-carboxylic acid sodium salt:

200 mg of 7-[2-(2-tritylaminothiazol-4-yl)-2-pivaloyloxyiminoacetamido]-3-methoxycarbonylmethyl-3-cefem-4-carboxylic acid diphenylmethyl ester was dissolved in 0.2 mL of anisole, to which 2 mL of trifluoroacetic acid was added while chilling on ice, followed by stirring for 30 min at the same temperature. The solution was concentrated under vacuum and powder was prepared by treating with isopropyl ether, which was dried and then dissolved in 2 mL of water-2 mL of acetic acid, and the pH was adjusted to 7.0 with a 2% aqueous sodium bicarbonate solution while chilling on ice. The aqueous layer was washed with ethyl acetate, followed by developing with 15 mL of Diaion HP-20. The target fraction was collected and freeze-dried, and 63 mg of the objective product was obtained.

IR: (Nujol): 1770 cm^{-1}

NMR (80 MHz, δ value, D2O)

1.15 (9H, s), 3.40-3.7 (7H, m), 5.0 (1H, d, J=4.8 Hz), 5.8 (1H, d, J=4.8 Hz), 6.8 (1H, s)

Application Example 6

7-[2-(2-aminothiazol-4-yl)-2-pivaloyloxyiminoacetamido]-3-(2-methoxycarbonylvinyl-3-cefem-4-carboxylic acid trifluoroacetic acid salt (syn isomer):

IR: (Nujol): 1770 cm^{-1}

NMR (80 MHz, δ value, PPM, DMSO-d_6)

1.20 (9H, s), 3.4 (2H, d), 3.6 (3H, s), 5.0 (1H, d, J=4.2 Hz), 5.7 (1H, d, J=12 Hz), 5.80 (1H, d. d, J=4.2 Hz, 9.6 Hz), 6.7 (1H, s), 6.8 (1H, d, J=12Hz)

Application Example 7 /15

7-[2-(2-tritylaminothiazol-4-yl)-2-acetyloxyiminoacetamido]-3-methylthio-3-cefem-4-carboxylic acid diphenylmethyl ester (syn isomer)

120 mg of 2-(2-tritylaminothiazol-4-yl)-2-acetyloxyiminoacetic acid (syn isomer) and 101 mg of 7-amino-3-methylthio-3-cefem-4-carboxylic acid diphenylmethyl ester were dissolved in 10 mL of dry methylene chloride, to which 33 mg of 1-hydroxybenztrizole was added. 1 mL of methylene chloride containing 50 mg of dicyclohexylcarbodiimide was added while chilling on ice, followed by stirring overnight at 5°C. The insoluble substance was removed and the solution was washed sequentially with a 2.5% aqueous hydrochloric acid solution and water, followed by concentrating. The residue was subjected to purification by silica gel

chromatography (Wako gel C-200, 8g, system: toluene-ethyl acetate) and 160 mg of the objective product was obtained.

IR: (Nujol): 1770, 1740-1710 cm^{-1}

NMR (80 MHz, δ value, PPM, $CDCl_3$)

2.20 (3H, s), 2.26 (3H, s), 3.54 (2H, b. s), 5.05 (1H, d, J=5.0 Hz), 5.75 (1H, d. d, J=5.0 Hz, 9.0 Hz), 7.86 (1H, s), 7.90 (1H, s), 7.00-7.45 (27H, m)

The compounds of Application Examples 8-11 were obtained in the same manner as in Application Example 7 using 2-(2-tritylaminothiazol-4-yl)-2-alkyacylloxyiminoacetic acids and corresponding 7-amino-3-cefem derivatives.

Application Example 8

7-[2-(2-tritylaminothiazol-4-yl)-2-propionoyloxyiminoacetamido]-3-methylthio-3-cefem-4-carboxylic acid diphenylmethyl ester (syn isomer)

IR: (Nujol): 1770, 1740-1710 cm^{-1}

NMR (80 MHz, δ value, PPM, $CDCl_3$)

1.25 (3H, t, J=8 Hz), 2.26 (3H, s), 2.48 (2H, q, J=8 Hz), 3.55 (2H, b. s), 5.06 (1H, d, J=5.0 Hz), 5.75 (1H, d. d, J=5 Hz, 9 Hz), 6.85 (1H, s), 6.92 (1H, s), 7.10-7.42 (27H, m)

Application Example 9

7-[2-(2-tritylaminothiazol-4-yl)-2-isobutyryloxyiminoacetamido]-3-methylthio-3-cefem-4-carboxylic acid diphenylmethyl ester (syn isomer)

NMR (80 MHz, δ value, PPM, $CDCl_3$)

1.20 (6H, d, J=8 Hz), 2.24 (3H, s), 2.70 (1H, m), 3.50 (2H, b. s), 5.06 (1H, d, J=5 Hz), 5.75 (1H, d. d, J=5 Hz, 10 Hz), 6.86 (1H, s), 6.90 (1H, s), 7.05-7.35 (27H, m)

Application Example 10

7-[2-(2-tritylaminothiazol-4-yl)-2-pivaloyloxyiminoacetamido]-3-methylthio-3-cefem-4-carboxylic acid diphenylmethyl ester (syn isomer)

NMR (80 MHz, δ value, PPM, $CDCl_3$)

1.27 (9H, s), 2.26 (3H, s), 3.35, 3.65 (2H, ABq, J=16 Hz), 5.03 (1H, d, J=5 Hz), 5.78 (1H, d. d, J=5 Hz, 9 Hz), 6.90 (1H, s), 6.95 (1H, s), 7.15-7.40 (27H, m)

Application Example 11

7-[2-(2-tritylaminothiazol-4-yl)-2-pivaloyloxyiminoacetamido]-3-ethylthio-3-cefem-4-carboxylic acid diphenylmethyl ester (syn isomer)

IR: (Nujol): 3300, 1780, 1740-1720 cm^{-1}

NMR (80 MHz, δ value, PPM, $CDCl_3$)

1.20 (3H, t, J=8 Hz), 1.25 (9H, s), 2.70 (1H, q, J=8 Hz), 3.45 (2H, b. s), 5.05 (1H, d, J=4.8 Hz), 5.70 (1H, d. d, J=4.8 Hz, 9.0 Hz), 6.85 (1H, s), 6.90 (1H, s), 7.15-7.32 (26H, b.s)

Application Example 12

7-[2-(2-tritylaminothiazol-4-yl)-2-acetyloxyiminoacetamido]-3-methylthio-3-cefem-4-carboxylic acid trifluoroacetic acid salt (syn isomer) /16

150 mg of 7-[2-(2-tritylaminothiazol-4-yl)-2-acetyloxyiminoacetamido]-3-methylthiol-3-cefem-4-carboxylic acid diphenylmethyl ester (syn isomer) was dissolved in 0.2 mL of anisole while chilling on ice. 2 mL of trifluoroacetic acid was further added at the same temperature, followed by stirring for 1 h while chilling on ice.

The solution in trifluoroacetic acid was concentrated under vacuum at 20°C and powder was prepared by treating the residue with isopropyl ether, which was separated by centrifuging after washing thoroughly with isopropyl ether and ether, and 55 mg of the objective product was obtained by drying under vacuum.

IR: (Nujol): 1770 cm^{-1}

NMR (80 MHz, δ value, PPM, DMSO-d_6)

2.16 (3H, s), 2.32 (3H, s), 3.75 (2H, s), 5.12 (1H, d, J=4.8 Hz), 5.68 (1H, d. d, J=4.8, J=7.5 Hz), 7.10 (1H, s), 9.78 (1H, d, J=7.5 Hz)

The compounds of Application Examples 13-16 were obtained in the same manner as in Application Example 12 by removing the protecting groups of the corresponding protected 3-cefem cephalosporin compounds.

Application Example 13

7-[2-(2-aminothiazol-4-yl)-2-propionoyloxyiminoacetamido]-3-methylthio-3-cefem-4-carboxylic acid trifluoroacetic acid salt (syn isomer)

IR: (Nujol): 1760 cm^{-1}

NMR (80 MHz, δ value, PPM, DMSO-d_6)

1.25 (3H, t, J=8 Hz), 2.26 (3H, s), 2.50 (2H, q, J=8 Hz), 5.05 (1H, d, J=5.0 Hz), 5.70 (1H, d. d, J=5.0 Hz, J=8.0 Hz), 7.05 (1H, s), 9.80 (1H, d, J=8.0 Hz)

Application Example 14

7-[2-(2-aminothiazol-4-yl)-2-isobutyryloxyiminoacetamido]-3-methylthio-3-cefem-4-carboxylic acid trifluoroacetic acid salt (syn isomer)

IR: (Nujol): 1760 cm^{-1}

NMR (80 MHz, δ value, PPM, DMSO-d_6)

1.15 (6H, d, J=7.5 Hz), 2.3 (3H, s), 2.65 (1H, m), 3.70 (2H, b.s), 5.15 (1H, d, J=5 Hz), 5.70 (1H, d. d, J=5 Hz, J=8.2 Hz), 7.05 (1H, s), 9.85 (1H, d, J=8.2 Hz)

Application Example 15

7-[2-(2-aminothiazol-4-yl)-2-pivaloyloxyiminoacetamido]-3-methylthio-3-cefem-4-carboxylic acid trifluoroacetic acid salt (syn isomer)

IR: (Nujol): 3300, 1770 cm^{-1}

NMR (80 MHz, δ value, PPM, DMSO-d_6)

1.20 (9H, s), 2.30 (3H, s), 3.75 (2H, b.s), 5.15 (1H, d, J=5 Hz), 5.70 (1H, d. d, J=5 Hz, J=9 Hz), 7.05 (1H, s), 9.85 (1H, d, J=9 Hz)

Application Example 16

7-[2-(2-aminothiazol-4-yl)-2-pivaloyloxyiminoacetamido]-3-ethylthio-3-cefem-4-carboxylic acid trifluoroacetic acid salt (syn isomer)

IR: (Nujol): 1760 cm^{-1}

NMR (80 MHz, δ value, PPM, DMSO-d_6)

1.20 (3H, t, J=8 Hz), 1.25 (9H, s), 2.70 (2H, q, J=8 Hz), 3.70 (2H, b.s), 5.15 (1H, d, J=5 Hz), 5.72 (1H, d. d, J=5 Hz, J=8 Hz), 7.1 (1H, s), 9.80 (1H, d, J=8 Hz)

Application Example 17

7-[2-(2-tritylaminothiazol-4-yl)-2-acetyloxyiminoacetamido]-3-methylthio-3-cefem-4-carboxylic acid pivaloyloxymethyl ester (syn isomer)

120 mg of 2-(2-tritylaminothiazol-4-yl)-2-acetyloxyiminoacetic acid (syn isomer) and 90 mg of 7-amino-3-methylthio-3-cefem-4-carboxylic acid pivaloyloxymethyl ester were dissolved in 10 mL of dry methylene chloride, to which 33 mg of 1-hydroxybenztrizole was added. 1 mL of methylene chloride containing 50 mg of dicyclohexylcarbodiimide was added while chilling on ice, followed by stirring overnight at 5°C. The insoluble substance was removed and the solution was washed sequentially with 2.5% aqueous hydrochloric acid and water, followed by drying and concentrating under vacuum. The residue was subjected to purification by silica gel chromatography and 130 mg of the objective product was obtained. /17

IR: (Nujol): 3300, 1770, 1740-1710 cm^{-1}

NMR (80 MHz, δ value, PPM, CDCl3)

1.20 (9H, s), 2.15 (3H, s), 2.3 (3H, s), 3.55 (2H, b. s), 5.05 (1H, d, J=4.8 Hz), 5.15-5.35 (3H, m), 6.85 (1H, s), 6.95 (1H, d, J=8 Hz), 7.15-7.35 (16H, m)

Application Example 18

7-[2-(2-tritylaminothiazol-4-yl)-2-pivaloyloxyiminoacetamido]-3-methylthio-3-cefem-4-carboxylic acid pivaloyloxymethyl ester (syn isomer)

The subject compound was obtained in the same manner as in Application Example 17 from corresponding 3-cefem compound.

NMR (80 MHz, δ value, PPM, CDCl3)

1.25 (9H, s), 1.30 (9H, s), 2.35 (3H, s), 3.55 (2H, b. d), 5.10 (1H, d, J=5 Hz), 5.60-5.95 (3H, m), 6.85 (1H, d, J=8 Hz), 6.95 (1H, s), 7.20-7.35 (16H, m)

Application Example 19

7-[2-(2-aminothiazol-4-yl)-2-acetyloxyiminoacetamido]-3-methylthio-3-cefem-4-carboxylic acid pivaloyloxymethyl ester (syn isomer)

100 mg of 7-[2-(2-tritylaminothiazol-4-yl)-2-acetyloxyiminoacetamido]-3-methylthio-3-cefem-4-carboxylic acid pivaloyloxymethyl ester (syn isomer) was dissolved in 0.1 mL of anisole while chilling on ice. Subsequently, 1 mL of trifluoroacetic acid was added, followed by stirring for 1 h at the same temperature, and the solution was concentrated under vacuum. Powder was prepared by treating the solution with isopropyl ether, which was thoroughly washed sequentially with isopropyl ether and ether. The powder was dissolved in 10 mL of ethyl acetate, and the pH was adjusted to 7.0 with a 5% aqueous sodium bicarbonate solution while chilling on ice. The organic layer was washed with water and dried over magnesium sulfate and 38 mg of the objective product was obtained after concentrating and drying.

IR: (Nujol): 1760 cm^{-1}

NMR (80 MHz, δ value, PPM, CDCl3)

1.25 (9H, s), 2.20 (3H, s), 2.35 (3H, s), 3.60 (2H, b. s), 5.10 (1H, d, J=5 Hz), 5.70-5.95 (3H, m), 6.90 (1H, s), 8.25 (1H, d, J=8 Hz)

Application Example 20

7-[2-(2-aminothiazol-4-yl)-2-pivaloyloxyiminoacetamido]-3-methylthio-3-cefem-4-carboxylic acid pivaloyloxymethyl ester (syn isomer)

The subject compound was obtained in the same manner as in Application Example 19.

NMR (80 MHz, δ value, PPM, CDCl3)

1.25 (9H, s), 1.30 (9H, s), 2.35 (3H, s), 3.65 (2H, b. s), 5.10 (1H, d, J=5 Hz), 5.70-5.95 (3H, m), 6.95 (1H, s), 7.60 (1H, d, J=8 Hz)

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（全 18 頁）

⑤4新規セフエム化合物

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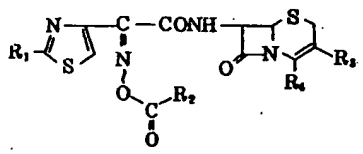
明　細　書

1. 発明の名称

新規セフエム化合物

2. 特許請求の範囲

1　一般式



〔式中、R_1はアミノ基または保護されたアミノ基、R_2はC_1～C_4の低級アルキル基、R_3はビニル基、低級アルキルチオ基、$-CH=CHCOOR_3'$（R_3'は水素又は低級アルキル基）又は$-CH_2COOR_3'$（R_3'は水素又は低級アルキル基）、R_4はカルボキシル基又は保護されたカルボキシル基を示す〕

で表わされるセフエム化合物及び医薬品として許容されるその塩類。

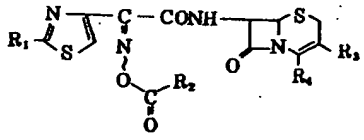
2　特許請求の範囲第1項記載の化合物のシン異性体。

3. 発明の詳細な説明

本発明は新規なセフエム化合物及びその医薬として許容される塩類に関する。

現在数多くのセファロスポリン系化合物が市販され、臨床に使用されているが、その中で経口投与可能なものはセファレキシン、セファトリジン、セファクロル、セフロキサジン等と数少ない。そこで本発明者らは広範囲の抗菌スペクトルを有しかも耐性菌に有効でかつ経口投与可能なセファロスポリン化合物の探索を意図し、セファロスポリン核の7位及び3位の種々の置換基を検討中に特定のセフエム化合物が広範囲の抗菌力を有し、しかも経口投与による感染治療効果が優れていることを見い出し本発明を完成させた。

すなわち、本発明は優れた抗菌活性を有する新規なセフエム化合物、更に詳しくは、次の一般式(I)



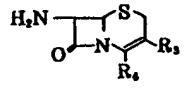
(I)

〔式中、R_1はアミノ基または保護されたアミノ基、R_2はC_1～C_4の低級アルキル基、R_3はビニル基、低級アルキルチオ基、$-CH=CHCOOR_5'$（R_5'は水素又は低級アルキル基）又は$-CH_2COOR_5'$（R_5'は水素又は低級アルキル基）、R_4はカルボキシル基又は保護されたカルボキシル基を示す〕

で表わされるセフエム化合物及び医薬品として許容されるその塩類を提供するものである。

本発明化合物(I)は、例えば次に示す何れかの方法によつて製造される。

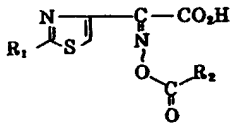
① 一般式(II)



(II)

（式中、R_3及びR_4は前記と同じ）

で表わされる化合物又はそのN－シリル誘導体に一般式(III)

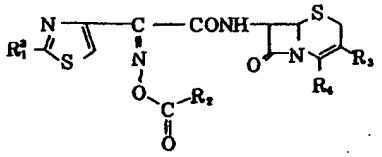


(III)

（式中、R_1及びR_2は前記と同じ）

で表わされる化合物又はそのカルボキシル基における反応性誘導体と反応させ、次いで要すれば保護基を除去することにより(I)式の本発明化合物を製造する。

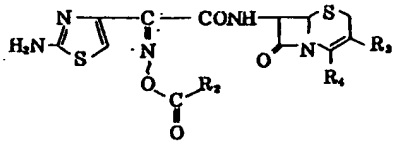
② 一般式(Ia)



(Ia)

（式中、R_1^aは保護されたアミノ基を示し、R_2，R_3及びR_4は前記と同じ）

で表わされる化合物を脱保護基として一般式(Ib)

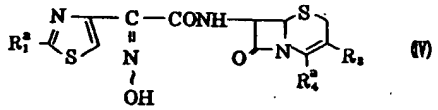


(Ib)

（式中、R_2，R_3及びR_4は前記と同じ）

で表わされる化合物を製造する。

③ 一般式(IV)



(IV)

（式中、R_4^aは保護されたカルボキシル基を示し、R_1^a及びR_3は前記と同じ）

で表わされる化合物に一般式(V)又は(VI)

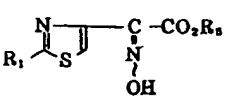
R_2COX (V)，R_2COCH_2X (VI)

（式中、Xはハロゲン原子を示し、R_2は前記と同じ）

で表わされる化合物を反応させ、次いで要すれば保護基を除去することにより(I)式の本発明化合物を製造する。

上記式(I)～(VI)において、「低級」とは特にことわらない限り炭素数1～4のものを意味する。R_1^aで表わされるアミノ保護基としては、所望により脱離できる通常の保護基であればよく、例えば2，2，2－トリクロロエトキシカルボニル基、2－メチルスルホニルエチルオキシカルボニル基、t－ブトキシカルボニル基、クロロアセチル基、トリチル基等が好適に使用される。R_4^aで表わされるカルボキシル保護基としては、β－ラクタム系化合物に通常使用されているものであればよく、例えばジフエニルメチル基、p－ニトロベンジル基、トリクロロエチル基、p－メトキシベンジル基、アリル基等が挙げられる。また、化合物(III)のカルボキシル基における反応性誘導体としては、例えば酸ハロゲン化物、酸アジド、酸無水物、混合酸無水物、活性アミド、活性エステル等が挙げられる。また、化合物(V)及び(VI)のハロゲン原子としては塩素、臭素又はヨウ素が挙げられる。

本発明方法①の原料である(III)式の化合物は、例えば一般式(VII)



(VII)

（式中、R_5はカルボキシル保護基を示し、R_1は前記と同じ）

で表わされる化合物に次式(V)又は(VI)、

R_2-COX (V) , R_2-COCH$_2$X (VI)

（式中、R_2及びXは前記と同じ）

で表わされる化合物を反応させ、次いでカルボキシル保護基を脱離させることにより製造される。

化合物(VII)と化合物(V)又は(VI)との反応は、塩基の存在下有機溶媒、水又は含水溶媒中で行われる。カルボキシル保護基の脱離は、オキシムのアシル基の開裂分解及びオキシムイミノ基の分解等が生起しない条件で行われなければならない。このためには、R_2としてアリル基を使用し、パラジウム触媒を用いて還元的に除去する方法（J. Org. Chem. 47-587, 1982年）、R_2としてt-ブチル基、p-メトキシベンジル基、ジフエニルメチル基を使用し、酸で加水分解する方法が採用される。

本発明方法①において、(III)式の化合物のカルボキシル基における反応性誘導体を使用する場合には、反応は、例えば水、アセトン、ジオキサン、アセトニトリル、クロロホルム、塩化メチレン、テトラヒドロフラン、酢酸エチル等の反応に悪影響を与えない溶媒中、氷冷下で行うのが好ましい。また、(III)式の化合物を遊離の形で使用するときは、縮合剤の存在下行うのが好ましい。この縮合剤としては、例えばN，N′-ジシクロヘキシルカルボジイミド；N-シクロヘキシル-N′-モルホリノエチルカルボジイミド；N-シクロヘキシル-N′-(4-ジエチルアミノシクロヘキシル)カルボジイミド；N，N′-ジエチルカルボジイミド；N，N′-ジイソプロピルカルボジイミド；N-エチル-N′-(3-ジメチルアミノプロピル)カルボジイミド；N，N′-カルボニルビス-(2-メチルイミダゾール)；ペンタメチレンケテン-N-シクロヘキシルイミン；ジフエニルケテン-N-シクロヘキシルイミン；エトキシアセチレン；1-アルコキシ-1-クロロエチレン；亜りん酸トリアルキル；ポリりん酸エチル；ポリりん酸イソプロピル；オキシ塩化りん；三塩化りん；塩化チオニル；塩化オキザリル；トリフエニルホスフィン；2-エチル-7-ヒドロキシベンズイソキサゾリウム塩；2-エチル-5-(m-スルホフエニル)イソキサゾリウムヒドロキシド分子内塩；1-(p-クロロベンゼンスルホニルオキシ)-6-クロロ-1H-ベンゾトリアゾールまたジメチルホルムアミドと塩化チオニル、ホスゲン、オキシ塩化りんなどとの反応によつて得られるいわゆるヴイルスマイヤー試薬などが挙げられる。

この反応はまた無機塩基または有機塩基の存在下に行なつてもよく、このような塩基の例としては、炭酸水素アルカリ金属（例えば炭酸水素ナトリウム、炭酸水素カリウムなど）、炭酸アルカリ金属（例えば炭酸ナトリウム、炭酸カリウムなど）、炭酸アルカリ土類金属（例えば炭酸カルシウムなど）、トリ(低級)アルキルアミン（例えばトリメチルアミン、トリエチルアミンなど）、ピリジン、N-(低級)アルキルモルホリン、N，N′-ジ(低級)アルキルベンジルアミンなどが挙げられる。

反応温度は特に限定されず、反応は通常冷却下ないし加温下に行なわれる。

本発明において、目的化合物(I)のシン異性体は化合物(II)と化合物(III)の対応するシン異性体とを、例えば前記ヴイルスマイヤー試薬の存在下に中性条件で反応させることによつて得ることができる。

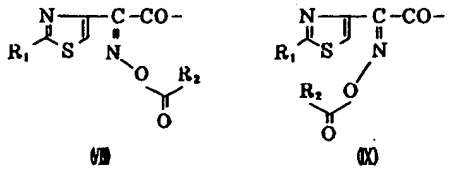
また、本発明方法③の反応は、自体公知の方法によつて行われる。すなわち、化合物(IV)と(V)の反応は、塩化メチレン、酢酸エチル、テトラヒドロフラン等の溶媒中、ピリジン、トリエチルアミン等の有機塩基又は炭酸カリウム、重炭酸ナトリウム等の無機塩基の存在下、-20～20℃の温度で行われる。また化合物(IV)と(VI)との反応は、ジメチルホルムアミド、ジメチルスルホキシド等の溶媒中0～5℃の温度で行うのが好ましい。

更にまた、本発明方法①～③の各方法において、保護基の除去は、その種類に応じて公知の方法、例えば酸による加水分解、アルカリによる加水分解、還元等の方法を採用できる。

本発明化合物(I)、(Ia)、(Ib)並びに原料化合物(III)、(IV)、(VII)にはシン異性体とアンチ異性体が存在するが、両異性体及びその混合物の何れも本発明

に含まれる。

ここで、目的化合物(I)において、シン異性体及びアンチ異性体とは、それぞれ次の部分構造(II)、(III)を有する幾何異性体を意味する。



(II)　　(III)

(式中、R_1及びR_2は前記と同じ)

本発明化合物は、遊離カルボキシル基又は/及び遊離アミノ基を有している場合には、常法によつて医薬として許容される塩類に導くことができる。当該塩類は通常の非毒性の塩であり、そのような塩としてはアルカリ金属塩(例えばナトリウム塩、カリウム塩など)およびアルカリ土類金属塩(例えばカルシウム塩、マグネシウム塩など)のような金属塩、アンモニウム塩、有機塩基との塩(例えばトリメチルアミン塩、トリエチルアミン塩、ピリジン塩、ピコリン塩、ジシクロヘキシルアミン塩、N,N'-ジベンジルエチレンジアミン塩など)、有機酸との塩(例えば酢酸塩、マレイン酸塩、酒石酸塩、メタンスルホン酸塩、ベンゼンスルホン酸塩、蟻酸塩、トルエンスルホン酸塩など)、無機酸との塩(例えば塩酸塩、臭化水素酸塩、硫酸塩、りん酸塩など)、またはアミノ酸との塩(例えばアルギニン塩、アスパラギン酸塩、グルタミン酸塩など)などが含まれる。

本発明の目的化合物(I)およびその医薬として許容される塩は新規化合物であり、強い抗菌活性を示し、グラム陽性菌及びグラム陰性菌を含む広い範囲の病原性微生物の発育を阻止し、特に経口投与用の抗菌剤として有用である。本発明の目的化合物(I)、またはその医薬として許容される塩を治療の目的で投与するにあたつては、上記化合物を有効成分として含有せしめ、医薬として許容される担体と混合して慣用の製剤の形で投与できる。担体としては、経口投与、非経口投与または外用に適した有機もしくは無機、固体もしくは液体の賦形剤を挙げることができる。また剤形としては、カプセル剤、錠剤、糖衣錠、軟膏、坐剤、溶液、懸濁液、乳剤などが挙げられる。

次にこの発明で提供される目的化合物の有用性を示すために、本発明の化合物のうち代表的なものについて、抗菌活性を調べた結果を示す。

1. 抗菌活性

(a) 試験方法

試験は寒天平板希釈法で行ない、第1表に示す各試験菌の増殖が起こらなくなる最小発育阻止濃度(MIC)を観察し記録した。結果を第1表に示す。

(b) 試験化合物

A：7-〔2-(2-アミノチアゾール-4-イル)-2-アセチルオキシイミノアセトアミド〕-3-メチルチオ-3-セフエム-4-カルボン酸トリフロロ酢酸塩(シン異性体)

B：7-〔2-(2-アミノチアゾール-4-イル)-2-ピバロイルオキシイミノアセトアミド〕-3-メチルチオ-3-セフエム-4-カルボン酸トリフロロ酢酸塩(シン異性体)

C：7-〔2-(2-アミノチアゾール-4-イル)-2-プロピオノイルオキシイミノアセトアミド〕-3-メチルチオ-3-セフエム-4-カルボン酸トリフロロ酢酸塩(シン異性体)

D：7-〔2-(2-アミノチアゾール-4-イル)-2-イソブチリルオキシイミノアセトアミド〕-3-メチルチオ-3-セフエム-4-カルボン酸トリフロロ酢酸塩(シン異性体)

E：7-〔2-(2-アミノチアゾール-4-イル)-2-ピバロイルオキシイミノアセトアミド〕-3-エチルチオ-3-セフエム-4-カルボン酸トリフロロ酢酸塩(シン異性体)

F：7-〔2-(2-アミノチアゾール-4-イル)-2-ピバロイルオキシイミノアセトアミド〕-3-メトキシカルボニ

ルメチル－3－セフエム－4－カルボン酸ナトリウム塩

G：7－〔2－（2－アミノチアゾール－4－イル）－2－ピバロイルオキシイミノアセトアミド〕－3－ビニル－3－セフエム－4－カルボン酸トリフロロ酢酸塩（シン異性体）

以下余白

試験菌	試験化合物						
	A	B	C	D	E	F	G
Sta. aureus 606	0.78	1.56	0.78	0.78	25	6.25	1.56
Sta. aureus 606 E 25	0.78	1.56	0.78	0.78	25	3.13	1.56
Sta. aureus 209P JC-1	0.20	0.39	0.20	0.39	6.25	1.56	0.39
Sta. aureus Smith (I)	0.20	0.78	0.20	0.39	12.5	1.56	0.78
Sta. epidermidis ATCC 14990	0.20	0.78	0.20	0.37	6.25	1.56	0.78
B. subilis ATCC 6633	0.39	0.78	0.39	0.39	12.5	3.13	0.78
E. coli W3630 RGN823	0.78	6.25	0.78	1.56	12.5	12.5	6.25
E. coli W3630 RGN14	0.78	12.5	1.56	3.13	12.5	25	6.25
E. coli W3630 RGN238	1.56	6.25	1.56	1.56	12.5	25	6.25
E. coli ML1410	0.78	12.5	1.56	3.13	12.5	25	12.5
E. clli NIHJ JC-2	0.78	3.13	0.78	1.56	12.5	12.5	6.25
E. coli No.29	0.39	3.13	0.78	0.78	12.5	6.25	3.13
Kleb. pneumoniae GN69	0.39	1.56	0.39	0.78	6.25	6.25	1.56
Kleb. pneumoniae GN118	0.39	3.13	0.39	0.78	6.25	12.5	3.13
Kleb. pneumoniae PCI602	0.78	3.13	0.39	0.78	6.25	12.5	3.13
Pro. mirabilis GN79	1.56	6.25	25	3.13	25	25	3.13
Pro. mirabilis GN310						12.5	25
Sal. typhi O-901-W	0.39	0.78	0.20	0.39	6.25	6.25	0.78

試験菌	試験化合物						
	A	B	C	D	E	F	G
Sal. typhimurium LT-2	0.39	3.13	0.39	0.78	12.5	12.5	1.56
Sal. enteritidis No.11	0.20	0.20	0.10	0.10	6.25	0.78	0.20
Shigella dysenteriae Shigae	0.20	0.78	0.20	0.39	6.25	3.13	0.78
Pro. vulgaris GN76	1.56	6.25	6.25	12.5	50	12.5	3.13
Pro. vulgaris GN106	0.78	3.13	1.56	3.13	50	12.5	3.13
Pro. vulgaris OX-19						12.5	12.5
Pro. morganii Kōno						25	50
Pro. rettgeri GN624	0.20	1.56	0.39	0.78	6.25	3.13	3.13
Pro. rettgeri J-0026	0.20	0.78	0.20	0.39	6.25	1.56	1.56
E. coli GN206						6.25	6.25
Citro. freundii GN346/16	1.51	6.25	0.78	1.56	12.5	25	6.25
Entero. cloacae G-0005						50	12.5
Entero. cloacae G-0008			6.25	6.25	25	25	6.25
Serr. marcescens No.1	1.51	6.25	3.13	3.13	25	25	6.25
Serr. marcescens No.2	3.13		3.13	3.13	25	50	12.5
Ps. cepacia M-0527	1.56	12.5	3.13	3.13	12.5	12.5	12.5
Str. faecalis W-75					12.5		

2. 感染治療実験

(a) 試験方法

試験は供試動物として、ICR-JCL系マウス（4週令雄、体重20±0.5g）のものを1群3匹として用いた。感染に用いた菌株はエシュリヒア・コリ（Escherichra Coli）Δ29であり、これをheart infusion agarにて37℃、20時間前培養後、生理食塩水にて懸濁し、muein を2.5%濃度になるよう混合した後、マウス腹腔内に注入した。薬剤サンプルは種々の濃度を菌感染直後に経口投与し、7日後のマウス生存数を観察した。結果を第2表に示す。

(b) 試験化合物

H：7-〔2-（2-アミノチアゾール-4-イル）-2-アセチルオキシイミノアセトアミド〕-3-メチルチオ-3-セフエム-4-カルボン酸ピバロイルオキシメチルエステル（シン異性体）

I：7-〔2-（2-アミノチアゾール-4-イル）-2-ピバロイルオキシイミノアセトアミド〕-3-メチルチオ-3-セフエム-4-カルボン酸ピバロイルオキシメチルエステル（シン異性体）

第 2 表

投与量（mg/マウス）	生存率						
	A*	B*	E*	H	I	セフロキサジン	無治療対照群
10	3/3	3/3	3/3	3/3	3/3	3/3	0/3
1	3/3	3/3	3/3	3/3	3/3	2/3	0/3
0.1	0/3	2/3	2/3	2/3	2/3	0/3	0/3

＊ 試験化合物A、B及びEは前記と同じ。

つぎに本発明を参考例及び実施例により詳細に説明するが、本発明はこれら実施例により限定されるものではない。

参考例1

エチル-2-（2-アミノチアゾール-4-イル）-2-ヒドロキシイミノアセテート（シン異

性体）：

氷酢酸３０mℓ中におけるアセト酢酸エチル３０gの溶液を撹拌し氷冷する。これに反応温度が10℃以下に維持される様な速度で、水４０mℓ中における亜硝酸ナトリウム１８gの溶液を加えた。約３０分間氷冷下撹拌し、ついで水８０mℓ中における塩化カリウム１６gの溶液を加えた。生成する混合物を１時間撹拌した。下層の有機層を分離し、そして水層をジエチルエーテルで抽出した。抽出物を油状物と合一し、水、飽和食塩水で順次洗浄し、乾燥させ濃縮乾固し、エチル－２－ヒドロキシイミノ－３－オキソブチレート（シン異性体）３０gを得た。塩化メチレン４０mℓ中エチル－２－ヒドロキシイミノ－３－オキソブチレート（シン異性体）1.5gの溶液を撹拌しそして氷冷する。これにスルフリルクロライド１４gを滴下し、２日間撹拌した。水洗した後、乾燥し濃縮した。残留油状物１７gをエタノール５０mℓ中に溶解し、そしてジメチルアニリン7.7mℓ、及びチオ尿素4.2gを撹拌しながら加えた。２時間後に生成物を戸取しエタノールで洗浄し乾燥し表記化合物７g得た。

mp　１８８℃（分解）

参考例２

エチル－２－（２－トリチルアミノチアゾール－４－イル）－２－ヒドロキシイミノアセテート塩酸塩（シン異性体）：

トリエチルアミン8.4mℓ含有ジメチルホルムアミド３０mℓ中における参考例１の生成物１３gの溶液を撹拌、冷却（－３０°）し、これに２時間かけてトリチルクロライド16.75gを加えた。混合物を同温度で３０分間撹拌後、室温で１７時間撹拌した。

次に水５００mℓと酢酸エチル５００mℓとの間に分配した。有機層を分離し水で洗浄しついで１Ｎ－HCβ５００mℓで撹拌した。析出する沈澱を集め、水、酢酸エチル、及びエーテルで順次洗浄し乾燥した。表記化合物を白色固体として１６.４g得た。

mp　１８４～１８６℃（分解）

参考例３

２－（２－トリチルアミノチアゾール－４－イル）－２－ヒドロキシイミノ酢酸ナトリウム塩（シン異性体）：

２－（２－トリチルアミノチアゾール－４－イル）－２－ヒドロキシイミノ酢酸エチル・塩酸塩（シン異性体）２０gをエタノール４００mℓに懸濁し、氷冷下１Ｎ－NaOH水溶液４００mℓを滴下する。室温下、２４時間撹拌後、析出する沈澱を戸取する。沈澱物をエーテルで洗浄後、テトラヒドロフラン５００mℓに懸濁し、氷冷下１０％ HCβでpH＝２.０に調整して、均一溶液を得る。次に氷冷下飽和重ソウ水でpH＝８.０に調整すると沈澱が析出する。戸取し水、エーテルで順次洗浄後乾燥する。白色粉末１６g得る。

参考例４

２－（２－トリチルアミノチアゾール－４－イル）－２－ヒドロキシイミノ酢酸アリルエステル（シン異性体）：

２－（２－トリチルアミノチアゾール－４－イル）－２－ヒドロキシイミノ酢酸ナトリウム塩1.8gをジメチルホルムアミド２０mℓに溶解し、これに氷冷下アリルアイオダイド0.８mℓを加え、室温下２４時間撹拌する。該反応液を酢酸エチル200mℓ－水２００mℓの混液に加え、有機層を水洗する（２００mℓ×２）。硫酸マグネシウムで乾燥後濃縮乾固し、このものを和光ゲルC－２００　６０gで精製する（系；トルエン－酢酸エチル）。収量1.３g。

NMR（８０MHz，δ値，PPM，CDCβ₃）；

4.85（2H, m），5.25～5.50（2H, m），5.95（1H, m），6.90（1H, s），7.85（16H, bs）

参考例５

２－（２－トリチルアミノチアゾール－４－イル）－２－アセチルオキシイミノ酢酸アリルエステル（シン異性体）：

２－（２－トリチルアミノチアゾール－４－イル）－２－ヒドロキシイミノ酢酸アリルエステル（シン異性体）４６９mgを乾燥塩化メチレン１０mℓに溶解し、氷冷下ピリジン0.１mℓを加える。次

にアセチルクロライド0.1 mlを含む乾燥塩化メチレン1 mlを滴下し、同温度で20分間攪拌する。水洗し硫酸マグネシウムで乾燥する。濃縮乾固後シリカゲルで精製し目的物500 mgを得る。

FD mass ; 511

IR (ヌジョール) ; 3300, 1740 cm^{-1}

NMR(80 MHz, δ値, PPM) ;

2.11(3H, s), 4.75~4.85(2H, m), 5.20~5.48(2H, m), 5.70~6.15(1H, m), 6.85(1H, s), 7.80(15H, s)

参考例5と同様にして、2-(2-トリチルアミノチアゾール-4-イル)-2-ヒドロキシイミノ酢酸アリルエステル(シン異性体)を対応する酸クロライドと反応させて、次の参考例6~8の化合物を得た。

参考例6

2-(2-トリチルアミノチアゾール-4-イル)-2-プロピノイルオキシイミノ酢酸アリルエステル(シン異性体):

FD mass ; 525

IR (ヌジョール) ; 3300, 1740 cm^{-1}

NMR(80 MHz, δ値, PPM) ;

1.25(3H, t, J=8Hz), 2.5(2H, q, J=8Hz), 4.75~4.85(2H, m), 5.20~5.48(2H, m), 5.70~6.15(1H, m), 6.82(1H, s), 7.80(15H, b.s)

参考例7

2-(2-トリチルアミノチアゾール-4-イル)-2-イソブチリルオキシイミノ酢酸アリルエステル(シン異性体):

FD mass ; 540

IR (ヌジョール) ; 3300, 1745 cm^{-1}

NMR(80 MHz, δ値, PPM)

1.20(6H, d, J=8Hz), 2.60(1H, m), 4.70~4.82(2H, m), 5.15~5.48(2H, m), 5.70~6.15(1H, m), 6.85(1H, s), 7.20(16H, s)

参考例8

2-(2-トリチルアミノチアゾール-4-イル)-2-ピバロイルオキシイミノ酢酸アリルエステル(シン異性体):

FD mass ; 553

IR (ヌジョール) ; 3300, 1740 cm^{-1}

NMR(80 MHz, δ値, PPM) ;

1.25(9H, s), 4.70~4.85(2H, m), 5.16~5.55(2H, m), 5.65~6.20(1H, m), 6.90(1H, s), 7.26(16H, s)

参考例9

2-(2-トリチルアミノチアゾール-4-イル)-2-アセチルオキシイミノ酢酸(シン異性体):

2-(2-トリチルアミノチアゾール-4-イル)-2-アセチルオキシイミノ酢酸アリルエステル(シン異性体)250 mgを乾燥塩化メチレン10 mlに溶解し、これに氷冷下2-エチルヘキサン酸カリウム85 mgを含む酢酸エチル溶液5 ml、更にトリフェニルホスフィン12 mg及びテトラキストリフェニルホスフィンパラジウム(0) 12 mgを加え、同温度で1時間攪拌する。次いで析出する沈殿を戸取し、イソプロピルエーテル、酢酸エチルで順次洗浄し乾燥して2-(2-トリチルアミノチアゾール-4-イル)-2-アセチルオキシイミノ酢酸カリウム塩を得る。ここで得たカリウム塩を酢酸エチル20 mlに懸濁し、氷冷下5% HCO_2 溶液でpH = 2.0に調整する。飽和食塩水で洗浄し乾燥する。濃縮乾固し目的生成物を白色粉末として130 mg得る。

NMR(80 MHz, δ値) ;

2.15(3H, s), 6.80(1H, s), 7.30(16H, bs)

参考例9と同様にして、対応する2-(2-トリチルアミノチアゾール-4-イル)-2-アルキルアシルオキシイミノ酢酸アリルエステル(シン異性体)を原料とし、パラジウム触媒の存在下2-エチルヘキサン酸カリウムを用いて次の参考例10~12の化合物を得た。

参考例10

2-(2-トリチルアミノチアゾール-4-イル)-2-プロピオノイルオキシイミノ酢酸:

NMR(80 MHz, δ値, PPM, $CDCO_2$) ;

1.25(3H, t, J=8Hz), 2.5(2H, q, J=8Hz), 6.80(1H, s), 7.30(16H, b.s)

参考例１１

２－（２－トリチルアミノチアゾール－４－イル）－２－イソプチリルオキシイミノ酢酸：

NMR（80 MHz，δ値，PPM，CDCℓ₃）；

1.05（6H，d，J＝8Hz），2.40（1H，m），6.85（1H，s），7.30（16H，b.s）

参考例１２

２－（２－トリチルアミノチアゾール－４－イル）－２－ピバロイルオキシイミノ酢酸：

NMR（80 MHz，δ値，PPM，CDCℓ₃）；

1.16（9H，s），6.80（1H，s），7.28（16H，bs）

参考例１３

７－β－フエニルアセタミド－３－メチルチオ－３－セフエム－４－カルボン酸－p－ニトロベンジルエステル：

乾燥アセトニトリル４０mℓに、７－β－フエニルアセタミド－３－ヒドロキシ－３－セフエム－４－カルボン酸－p－ニトロベンジルエステル5.6ｇ（１２mM）を懸濁させ、撹拌しながら窒素雰囲気下－２０℃に冷却し、ジイソプロピル－エチルアミン２.４mℓ及びジフエニル－クロロホスフエート２.８mℓを加えた。反応混合物を約３０分間同温度で撹拌し、透明溶液を得た。ＴＬＣで反応終了を確認後、反応液を－３０℃に冷却し、ジイソプロピル－エチルアミン２.４mℓを加え、メチル－メルカプタン約３ｇを撹拌下に吹込んだ。－２５～－３０℃で約２時間撹拌しながら反応を続け（結晶析出）、ＴＬＣで反応終了を確認した後、酢酸０.５mℓを加えた。

生成物を集め、冷アセトニトリル７mℓ、イソプロピルエーテル１０mℓで順次洗浄後、真空乾燥した。収量；４.９５ｇ（収率；８３％）。

mp；２３１℃（分解）

IR（ヌジョール）；3230，1775（β－ラクタム），1705，1650cm⁻¹

UV λ_{max}；３１９ nm。

NMR（DMSO－d_6＋CDCℓ₃）；δ値（60 MHz）

3.28（3H，s），3.61（2H，s），3.68（2H，s），5.03（1H，d，（J＝4.6Hz）），5.73（2H，s），5.64（1H，dd，（J＝4.6，J＝7.8Hz）），7.29（5H，s），7.63，8.20（4H，2×d，（J＝8.2）），8.83（1H，d，（J＝7.8））。

参考例１４

７－フエニルアセタミド－３－メチルチオ－３－セフエム－４－カルボン酸：

７－フエニルアセタミド－３－メチルチオ－３－セフエム－４－カルボン酸－p－ニトロベンジルエステル〔mp.２３１℃（分解）〕2.5ｇをジオキサン１５mℓ、８５％ギ酸１０mℓに加え、５０～５５℃に加温し、撹拌下に亜鉛末1.5～３ｇを数回に分けて加え、２～５時間反応させる。薄層クロマトグラフイ（ＴＬＣ）で反応終了を確めた後、室温に冷し、不溶物を集め、ジオキサンで洗う。反応液と洗液を合わせ、減圧で溶媒の大部分を留去する。酢酸エチル１０mℓ、氷水５０mℓ中に撹拌しながら、炭酸水素ナトリウム液でpH 7.0～7.5に調整しつつ、反応液を少量づつ滴下する。全量添加後、不溶物を集め水洗する。水層および洗液を合わせ、酢酸エチルで数回抽出する。有機層は少量の水で水洗し、水層を合わせ、必要があれば、活性炭処理をする。水層は塩酸でpH １～２に調整し、一夜氷室におく。固形物を集め、水洗後、少量のイソプロピルエーテルで洗い乾燥して、標題の化合物を得た。収量；1.４ｇ（７７％）。アセトン＋イソプロピルエーテルから再結晶。

mp １９７～９８℃（分解）

UV λ_{max}；３１８ nm（９５％エタノール）

IR（ヌジョール）；3280（NH），1770（β－ラクタム），1690，1640cm⁻¹

NMR（DMSO－d_6＋CDCℓ₃）；δ値〔60 MHz（R600）〕

2.33（3H，s），3.57（2H，s），3.67（2H，s），5.01（1H，d，J＝4.7Hz），5.56（1H，dd，J＝4.7，8.2Hz），7.25（5H，s），9.01（1H，d，J＝8.2Hz）

参考例１５

７－フエニルアセタミド－３－メチルチオ－３－セフエム－４－カルボン酸ジフエニルメチルエステル：

参考例１４で得られた７－フエニルアセタミド－３－メチルチオ－３－セフエム－４－カルボン

酸1.82gをアセトンに温めて溶かす。撹拌しながらジアゾジフエニルメタンのn-ヘキサン溶液を加える。TLCで反応を追跡しながら室温で一夜反応させた後、減圧濃縮し乾固する。過剰のジアゾジフエニルメタンをn-ヘキサンで処理して除く。固形物を塩化メチレンに溶し、酸性炭酸ソーダ水でpH 7.5に調整した。塩化メチレン層を分取し、乾燥後減圧濃縮乾固し、固形物をイソプロピルエーテル、エチルエーテルで処理して乾燥し、標題の化合物を得た。収量：2.4g（90%）。アセトン+メタノールから再結晶。

mp 162～63℃（分解）

UV λ_{max} ：318 nm（95%エタノール）

IR（ヌジョール）：3230(NH), 1780(β-ラクタム), 1700(エステル), 1650 cm^{-1}

NMR(CDCl$_3$) ：δ値（60 MHz）

1.99(3H, s), 2.91, 3.38(2H, ABq, J=16.8Hz), 3.64(2H, s), 4.95(1H, d, J=4.3Hz), 5.62(1H, d, d, J=4.3, 8.6Hz), 6.86(1H, s), 7.2～7.33(16H)

参考例16

7-アミノ-3-メチルチオ-3-セフエム-4-カルボン酸ジフエニルメチルエステル塩酸塩：

参考例15で得られた7-フエニルアセタミド-3-メチルチオ-3-セフエム-4-カルボン酸ジフエニルメチルエステル2.65gを塩化メチレン50mlに溶かし、-30℃に冷す。これに無水ピリジン4mlを加え、さらに五塩化リンの微粉末3.2gを投入する。徐々に昇温させ、-10～10℃で約3時間撹拌する。TLCで反応終了を確かめた後-40℃に冷す。（反応液の一部をとり、無水メタノールを加え、ベンゼン：酢酸エチル＝2：1で展開する。）この反応液（結晶析出）に撹拌下、無水メタノール15mlを滴下する。透明な反応液は、徐々に昇温させ、-10℃で約1時間撹拌する。TLCで反応終了を確かめた後、40mlの冷食塩水中に加え、撹拌下、希アンモニア水でpH 1.5～2.0に保ちながら氷冷下約1時間反応させる。析出物を集め、少量の氷水、酢酸エチル、イソプロピルエーテルの順に洗い、乾燥して標題の化合物を得た。収量：2.25g（91%）。

mp 203～205℃（分解）

UV λ_{max} ：319 nm（95%エタノール）

IR（ヌジョール）：1780（β-ラクタム）, 1760, 1700 cm^{-1}

NMR(DMSO-d_6)：δ値（60 MHz）

2.44(3H, s), 3.73, 4.13(2H, ABq, J=16Hz), 5.08(1H, d, J=4.3Hz), 5.28(1H, d, J=4.3Hz), 6.90(1H, s), 7.20～7.80(13H, m)

参考例17

7-アミノ-3-エチルチオ-3-セフエム-4-カルボン酸ベンズヒドリルエステル塩酸塩：

参考例13～16に準じて表記化合物を得た。

mp 172～173℃（分解）

UV λ_{max} ：319 nm（95%エタノール）

IR（ヌジョール）：1778, 1705 cm^{-1}

NMR(DMSO-d_6)：δ値（60 MHz）

1.16(3H, t, J=7Hz), 2.93(2H, q, J=7Hz), 2.93(2H, q, J=7Hz), 3.68, 4.10(2H, ABq, J=15Hz), 5.05(1H, d, J=5Hz), 5.77(1H, d, J=5Hz), 6.83(1H, s), 7.3(10H, m)

参考例18

7-フエニルアセトアミド-3-ビニル-3-セフエム-4-カルボン酸ジフエニルメチルエステル：

7-フエニルアセトアミド-3-ブロムメチル-3-セフエム-4-カルボン酸ジフエニルメチルエステル1.2gをジメチルホルムアミド2mlに溶解し、これにトリフエニルホスフイン818mg及びヨウ化ナトリウム311mgを加え、0～5℃で17時間撹拌する。反応液をイソプロピルエーテルで洗浄して粉末化し、更に酢酸エチルで洗浄する。得られた粉末を塩化メチレン30mlに懸濁し、これに氷冷下36%ホルムアルデヒド溶液15mlを加える。次いで飽和炭酸水素ナトリウム水溶液でpH＝9.0に調整し、氷冷下30分、室温で2時間撹拌する。更に氷冷下5% HClでpH＝5.0に

調整し塩化メチレンで抽出する。水洗後、硫酸マグネシウムで乾燥する。減圧乾固しシリカゲルクロマトで精製する。（和光ゲルC－200 40g、系トルエン酢酸エチル）目的物420mgを得る。

IR（ヌジョール）；1765，1710 cm^{-1}

NMR（80 MHz，δ値，PPM，$CDCl_3$）；

3.30，3.60（2H，ABq，J＝19Hz），3.56（2H，s），4.91（1H，d，J＝4.8Hz），5.16（1H，d，J＝8Hz），5.36（1H，d，J＝15Hz），5.75（1H，d．d，J＝4.8，9.0Hz），6.25（1H，d，J＝9.0Hz）6.89（1H，s），7.10～7.55（16H，m）

参考例19

7－アミノ－3－ビニル－3－セフエム－4－カルボン酸ジフエニルメチルエステル塩酸塩：

7－フエニルアセトアミド－3－ビニル－3－セフエム－4－カルボン酸ベンズヒドリルエステル230mgを乾燥塩化メチレン10mlに溶解し－40℃に冷却する。これにピリジン0.36ml及び五塩化リン282mgを加え－40℃で2時間、481mg（0.0001モル）を塩化メチレン20mlに溶かし、ピリジン0.40mlを加え－20℃に冷す。これに五塩化リン440mgを加え撹拌下徐々に昇温させ＋5～＋10℃で約90分反応させる（五塩化リンの消失後30分反応）。反応液を－30℃に冷し、撹拌下イソプタノール2.0mlの塩化メチレン5ml液を滴下する。ついで徐々に昇温させ、＋5～＋10℃で2時間反応させた（TLCで反応を追跡する）。反応終了後0℃に冷し、食塩水2mlを含む冷水5ml中に撹拌下そそぐ。氷冷下約60分撹拌し、これにジイソプロピルエーテル10ml、エチルエーテル10mlを加えた。まもなく白色晶析出が増えた。この結晶を集め、ジイソプロピルエーテル、エーテルで洗い乾燥した。収量360mg。

mp 148～50℃（分解）

UV λ_{max} ；321 nm （95％エタノール）

IR（ヌジョール）；1781，1762，1700 cm^{-1}

参考例21

7－アミノ－3－エチルチオ－3－セフエム－4－カルボン酸－エトキシ－カルボニルオキシエチルエステル塩酸塩：

7－フエニルアセタミド－3－エチルチオ－3－セフエム－4－カルボン酸エトキシカルボニルオキシエチルエステル（mp 130～31℃）990mg（0.0002モル）を用い、他は参考例20と同様に反応させ処理した。標題の化合物を750mg（90.8％）得た。

mp 188～90℃（分解）

UV λ_{max} ；320 nm （95％エタノール）

IR（ヌジョール）；1780，1763，1710 cm^{-1}

参考例22

7－フエニルアセトアミド－3－メトキシカルボニルメチル－3－セフエム－4－カルボン酸p－ニトロベンジルエステル：

7－フエニルアセトアミド－3－ヒドロキシ－3－セフエム－4－カルボン酸 p－ニトロベンジルエステル4.7gをジメチルホルムアミド35mlに溶解し、これにカルボメトキシメチレントリフエニルホスホラン4gを加え室温で24時間撹

拌する。反応液を濃縮し、酢酸エチル５００mlに溶解し、冷５％HCl、水、飽和食塩水で順次洗浄し硫酸マグネシウムで乾燥する。次いで減圧下濃縮乾固し、残渣を和光ゲルC－２００（２００g）でカラムクロマト精製する（系；トルエン－酢酸エチル）目的物２８gを得る。

IR（ヌジョール）；3300，1760cm^{-1}

NMR（80 MHz，δ値，PPM，$CDCl_3$）

3.20～3.75（9H，m），5.00（1H，d，J＝4.8Hz），5.30（2H，b.s），5.85（1H，d.d，J＝4.8Hz，9Hz），6.15（1H，d，J＝9Hz），7.35（5H，s），7.55，8.22（4H，ABq，J＝9Hz）

上記反応中、副産物（セファロスポリン核二重結合の異性体）８８２mgを得た。この物は常法により過酸で酸化し三塩化リンで還元すると表記目的物と同一物性の物質となつた。

参考例２３

７－フエニルアセトアミド－３－メトキシカルボニルメチル－３－セフエム－４－カルボン酸ジフエニルメチルエステル：

７－フエニルアセトアミド－３－メトキシカルボニルメチル－３－セフエム－４－カルボン酸p－ニトロベンジルエステル2.8gをギ酸５０ml及びエタノール５０ml中に氷冷下に溶解する。攪拌下、亜鉛粉1.8gを１０分間かけて加える。室温で1時間、５０℃で2時間攪拌し不溶物を戸取する。戸液を減圧下に濃縮し酢酸エチル５０ml－水２０mlの混液に加える。氷冷下飽和炭酸水素ナトリウム水でpH＝7.0に保つ。不溶物を除去し水層を酢酸エチルで洗浄する。水層を５％HClで氷冷下pH＝2.0に調整し、酢酸エチルで抽出する。

有機層にジフエニルジアゾメタン－n－ヘキサン溶液を加え室温で反応させる。原料（カルボン酸）が消失したら減圧下濃縮乾固し、残渣をイソプロピルエーテルで洗浄し、目的物1.27gを得る。

IR（ヌジョール）；3320，1770cm^{-1}

NMR（80 MHz，δ値，$CDCl_3$）；

3.32～3.70（9H，m），4.95（1H，d，J＝4.8Hz），5.80（1H，d.d，J＝4.8Hz，9.6Hz），6.10（1H，d，J＝9.6Hz），6.85（1H，s），7.15～7.35（16H，m）

参考例２４

７－アミノ－３－メトキシカルボニルメチル－３－セフエム－４－カルボン酸ジフエニルメチルエステル：

五塩化リン1.12gを塩化メチレン２０mlに溶解し、氷冷下ピリジン1.45mlを加える。同温度で３０分間攪拌し－５０℃に冷却する。次いで７－フエニルアセトアミド－３－メトキシカルボニルメチル－４－カルボン酸ジフエニルメチルエステル1.0gを含む塩化メチレン１０mlを加え－５０℃にて2時間、氷冷下にて2時間攪拌する。－５０℃に冷却し、乾燥メタノール4mlを滴下する。０℃で1時間攪拌して氷冷下２０mlの飽和食塩水を加え同温度で３０分攪拌する。塩化メチレンで抽出し飽和食塩水で洗浄後氷冷下炭酸水素ナトリウム水でpH＝7.0に調整する。乾燥後濃縮乾固し和光ゲルC－２００　１５gで精製する（系；トルエン－酢酸エチル）目的物３５０mgを得る。

IR（ヌジョール）；1780cm^{-1}

NMR（80 MHz，δ値，$CDCl_3$）；

1.70（2H，b.s），3.36～3.65（7H，m），4.70（1H，d，J＝4.8Hz），4.96（1H，d，J＝4.8Hz），6.90（1H，s），7.20～7.40（10H，m）

参考例２５

７－フエニルアセトアミド－３－メトキシカルボニルビニル－3－セフエム－４－カルボン酸ジフエニルメチルエステル：

７－フエニルアセトアミド－３－ブロムメチル－３－セフエム－４－カルボン酸ジフエニルメチルエステル1.2gをジメチルホルムアミド2mlに溶解し、これにトリフエニルホスフイン８１８mg及びヨウ化ナトリウム３１１mgを加え、５℃で20時間攪拌する。減圧下濃縮しイソプロピルエーテルで粉末化し、更に酢酸エチルで洗浄する。

得られた塩を塩化メチレン３０mlに溶解し、これにメチルグリオキザレート・一水和物５８０mgを加え、氷冷下飽和炭酸水素ナトリウム水でpH

＝9に調整し、室温で4時間撹拌する。次いで、氷冷下5%塩酸水でpH＝5.0に調整し塩化メチレンで抽出する。水洗後硫酸マグネシウムで乾燥し濃縮乾固する。和光ゲルC－200　20gで精製（系；トルエン－酢酸エチル）し、目的物184mgを得る。

IR（ヌジョール）；1780 cm^{-1}

NMR（80 MHz，δ値，PPM，CDCℓ_3）；

3.40～3.65（7H，m），5.0（1H，d，J＝4.2Hz），6.70（1H，d，J＝12Hz），6.8（1H，d.d，J＝4.2Hz，9.6Hz），6.15（1H，d，J＝9.6Hz），6.80（1H，s），6.82（1H，d，J＝12Hz），7.20～7.40（16H，m）

参考例26

7－アミノ－3－メトキシカルボニルビニル－3－セフエム－4－カルボン酸ジフエニルメチルエステル：

窒素気流下、五塩化リン164mgを塩化メチレン2mlに溶解し、これに氷冷下ピリジン0.21mlを加え、同温度で30分撹拌する。他方7－フェニルアセトアミド－3－メトキシカルボニルビニル－3－セフエム－4－カルボン酸ジフエニルメチルエステル150mgを含む塩化メチレン1.5mlを先に調製した溶液中に－50℃で滴下する（約10分間）。－50℃で30分間、0～5℃で2時間撹拌後－50℃に冷却し、反応液を－50℃に冷却したメタノール2ml中に滴加する。次いで－50℃で30分間、0～5℃で1時間撹拌後、飽和食塩水3mlを加え、同温度で30分撹拌する。塩化メチレンで抽出し飽和食塩水で洗浄する。飽和食塩水の存在下2%炭酸水素ナトリウム水でpH＝7.0に調整し水洗する。硫酸マグネシウムで乾燥し濃縮乾固する。和光ゲルC－200　2gで精製（系；トルエン－酢酸エチル）し、目的物73mgを得た。

IR（ヌジョール）；1780 cm^{-1}

NMR（80 MHz，δ値，PPM，CDCℓ_3）；

1.75（2H，b.s），3.40（2H，b.s），3.56（3H，s），4.7（1H，d，J＝4.2Hz），4.9（1H，d，J＝4.8Hz），5.75（1H，d，J＝12Hz），6.85（1H，d，J＝12Hz），6.90（1H，s），7.2～7.4（10H，m）

実施例1

7－〔2－（2－トリチルアミノチアゾール－4－イル）－2－ピバロイルオキシイミノアセトアミド〕－3－ビニル－3－セフエム－4－カルボン酸ジフエニルメチルエステル（シン異性体）：

2－（2－トリチルアミノチアゾール－4－イル）－2－ピバロイルオキシイミノ酢酸（シン異性体）192mg、7－アミノ－3－ビニル－3－セフエム－4－カルボン酸ジフエニルメチルエステル120mg、及び1－ヒドロキシベンズトリアゾール50mgを塩化メチレン10mlに溶解し氷冷する。ジシクロヘキシルカルボジイミド75mgを含む塩化メチレン1mlを加え5℃で終夜撹拌する。減圧下濃縮し、酢酸エチル50mlに溶解する。不溶物を除去し冷5%塩酸水、飽和食塩水で順次洗浄する。硫酸マグネシウムで乾燥後、減圧下濃縮乾固する。和光ゲルC－200　8g（系；トルエン－酢酸エチル）で精製し目的物200mgを得た。

IR（ヌジョール）；1770，1740～1710 cm^{-1}

NMR（80 MHz，δ値，PPM，CDCℓ_3）；

1.30（9H，s），3.50（2H，b.s），5.05（1H，d.J＝5Hz），5.20（1H，d，J＝8Hz），5.40（1H，d，J＝14.5Hz），5.90（1H，d.d，J＝5Hz，J＝9.5Hz），6.90（2H，b.s），6.65～7.10（1H，m），7.15～7.40（26H，m）

実施例2

7－〔2－（2－トリチルアミノチアゾール－4－イル）－2－アセチルオキシイミノアセトアミド〕－3－ビニル－3－セフエム－4－カルボン酸ジフエニルメチルエステル（シン異性体）：

実施例1と同様にして、2－（2－トリチルアミノチアゾール－4－イル）－2－アセチルオキシイミノ酢酸を原料として標記化合物を得た。

IR（ヌジョール）；3300，1770 cm^{-1}

NMR（80 MHz，δ値，PPM，CDCℓ_3）；

2.70（3H，s），5.0（1H，d，J＝4.8Hz），5.2（1H，d，J＝10Hz），5.4（1H，d，J＝16Hz），5.8（1H，d，d，J＝4.8Hz，J＝9.0Hz），6.8（1H，

s), 6.9(1H, s), 7.1~7.3(27H, m)

実施例3

7-〔2-(2-アミノチアゾール-4-イル)-2-ピバロイルオキシイミノアセトアミド〕-3-ビニル-3-セフエム-4-カルボン酸トリフロロ酢酸塩(シン異性体):

7-〔2-(2-トリチルアミノチアゾール-4-イル)-2-ピバロイルオキシイミノアセトアミド〕-3-ビニル-3-セフエム-4-カルボン酸ジフエニルメチルエステル(シン異性体)200mgをアニソール0.4mlに溶解し、氷冷下、冷トリフロロ酢酸4mlを加え同温度で1時間撹拌する。減圧下濃縮しイソプロピルエーテルで粉末化、洗浄して乾燥する。目的物85mgを得る。

IR(ヌジョール): 1760cm^{-1}

NMR(80 MHz, δ値, PPM, DMSO-d_6):
1.15(9H, s), 3.50, 3.86(2H, ABq, J=17.6Hz), 5.16(1H, d, J=5Hz), 5.35(1H, d, J=9Hz), 5.60~5.78(2H, m), 6.75~7.10(1H, m), 6.95(1H, s)

実施例4

7-〔2-(2-トリチルアミノチアゾール-4-イル)-2-ピバロイルオキシイミノアセトアミド〕-3-メトキシカルボニルメチル-3-セフエム-4-カルボン酸ジフエニルメチルエステル(シン異性体):

2-(2-トリチルアミノチアゾール-4-イル)-2-ピバロイルオキシイミノ酢酸256mg、7-アミノ-3-メトキシカルボニルメチル-3-セフエム-4-カルボン酸ジフエニルメチルエステル181mg、及び1-ヒドロキシベンズトリアゾール67mgを塩化メチレン20mlに溶解し氷冷する。ジシクロヘキシルカルボジイミド103mgを含む塩化メチレン1mlを加え5℃で終夜撹拌する。減圧下濃縮し、酢酸エチル30mlに溶解し不溶物を除去する。冷5%塩酸水、飽和食塩水で順次洗浄し乾燥する。減圧下濃縮乾固し残渣を和光ゲルC-200 15gで精製する(系:トルエン-酢酸エチル)。目的物100mgを得た。

IR(ヌジョール): 3300, 1780cm^{-1}

NMR(80 MHz, δ値, PPM, $CDCl_3$):
1.16(9H, s), 3.40~3.70(7H, m), 5.10(1H, d, J=5Hz), 5.8(1H, d, d, J=5Hz, J=9.6Hz), 6.8(1H, s), 6.85(1H, s), 7.2~7.4(26H, m)

実施例5

7-〔2-(2-アミノチアゾール-4-イル)-2-ピバロイルオキシイミノアセトアミド〕-3-メトキシカルボニルメチル-3-セフエム-4-カルボン酸ナトリウム塩:

7-〔2-(2-トリチルアミノチアゾール-4-イル)-2-ピバロイルオキシイミノアセトアミド〕-3-メトキシカルボニルメチル-3-セフエム-4-カルボン酸ジフエニルメチルエステル200mgをアニソール0.2mlに溶解し、これに氷冷下トリフロロ酢酸2mlを加え、同温度で30分間撹拌する。次いで減圧下濃縮し、イソプロピルエーテルで粉末化し乾燥したのち、これを水2ml-酢酸2mlに溶解し、氷冷下2%炭酸水素ナトリウム水でpH=7.0に調整する。水層を酢酸エチルで洗浄後、ダイヤイオンHP-20 15mlに展開し精製する。目的フラクションを集め凍結乾燥し、目的物63mgを得た。

IR(ヌジョール): 1770cm^{-1}

NMR(80 MHz, δ値, D_2O):
1.15(9H, s), 3.40~3.7(7H, m), 5.0(1H, d, J=4.8Hz), 5.8(1H, d, J=4.8Hz), 6.8(1H, s)

実施例6

7-〔2-(2-アミノチアゾール-4-イル)-2-ピバロイルオキシイミノアセトアミド〕-3-(2-メトキシカルボニルビニル-3-セフエム-4-カルボン酸トリフロロ酢酸塩(シン異性体):

IR(ヌジョール): 1770cm^{-1}

NMR(80 MHz, δ値, PPM, DMSO-d_6):
1.20(9H, s), 3.4(2H, d), 3.6(3H, s), 5.0(1H, d, J=4.2Hz), 5.7(1H, d, J=12Hz), 5.80(1H, d, d, J=4.2Hz, 9.6Hz), 6.7(1H, s), 6.8(1H, d, J=12Hz)

実施例7

7-〔2-(2-トリチルアミノチアゾール-4-イル)-2-アセチルオキシイミノアセトアミド〕-3-メチルチオ-3-セフエム-4-カルボン酸ジフエニルメチルエステル(シン異性体):

2-(2-トリチルアミノチアゾール-4-イル)-2-アセチルオキシイミノ酢酸(シン異性体)120mg及び7-アミノ-3-メチルチオ-3-セフエム-4-カルボン酸ジフエニルメチルエステル101mgを乾燥塩化メチレン10mlに溶解し、これに1-ヒドロキシベンズトリアゾール33mgを加える。氷冷下、ジシクロヘキシルカルボジイミド50mgを含む塩化メチレン1mlを加え5℃で終夜撹拌する。不溶物を戸取し2.5% HCl水、水で順次洗浄後濃縮乾固する。シリカゲルクロマトで精製する。(和光ゲルC-200 8g、系;トルエン-酢酸エチル)。目的物160mgを得る。

IR(ヌジョール);1770, 1740~1710 cm^{-1}

NMR(80 MHz, δ値, PPM, $CDCl_3$);

6.85(1H, s), 6.92(1H, s), 7.10~7.42(27H, m)

実施例9

7-〔2-(2-トリチルアミノチアゾール-4-イル)-2-イソブチリルオキシイミノアセトアミド〕-3-メチルチオ-3-セフエム-4-カルボン酸ジフエニルメチルエステル(シン異性体):

NMR(80 MHz, δ値, PPM, $CDCl_3$);

1.20(6H, d, J=8Hz), 2.24(3H, s), 2.70(1H, m), 3.50(2H, b.s), 5.06(1H, d, J=5Hz), 5.75(1H, d. d, J=5Hz, 10Hz), 6.86(1H, s), 6.90(1H, s), 7.05~7.35(27H, m)

実施例10

7-〔2-(2-トリチルアミノチアゾール-4-イル)-2-ピバロイルオキシイミノアセトアミド〕-3-メチルチオ-3-セフエム-4-カルボン酸ジフエニルメチルエステル(シン異性体):

2.20(3H, s), 2.26(3H, s), 3.54(2H, b.s), 5.05(1H, d, J=5.0Hz), 5.75(1H, d. d, J=5.0Hz, 9.0Hz), 7.86(1H, s), 7.90(1H, s), 7.00~7.45(27H, m)

実施例7と同様に2-(2-トリチルアミノチアゾール-4-イル)-2-アルキルアシルオキシイミノ酢酸及び対応する7-アミノ-3-セフエム-誘導体を用いて実施例8~11の化合物を得る。

実施例8

7-〔2-(2-トリチルアミノチアゾール-4-イル)-2-プロピオノイルオキシイミノアセトアミド〕-3-メチルチオ-3-セフエム-4-カルボン酸ジフエニルメチルエステル(シン異性体):

IR(ヌジョール);1770, 1740~1710 cm^{-1}

NMR(80 MHz, δ値, PPM, $CDCl_3$);

1.25(3H, t, J=8Hz), 2.26(3H, s), 2.48(2H, q, J=8Hz), 3.55(2H, b.s), 5.06(1H, d=5Hz), 5.75(1H, d. d, J=5Hz, 9Hz),

NMR(80 MHz, δ値, PPM, $CDCl_3$);

1.27(9H, s), 2.26(3H, s), 3.35, 3.65(2H, ABq, J=16Hz), 5.03(1H, d, J=5Hz), 5.78(1H, d. d, J=5Hz, 9Hz), 6.90(1H,s), 6.95(1H, s), 7.15~7.40(27H, m)

実施例11

7-〔2-(2-トリチルアミノチアゾール-4-イル)-2-ピバロイルオキシイミノアセトアミド〕-3-エチルチオ-3-セフエム-4-カルボン酸ジフエニルメチルエステル(シン異性体):

IR(ヌジョール);3300, 1780, 1740~1720 cm^{-1}

NMR(80 MHz, δ値, PPM, $CDCl_3$);

1.20(3H, t, J=8H), 1.25(9H, s), 2.70(2H, q, J=8Hz), 3.45(2H, b.s), 5.05(1H, d, J=4.8Hz), 5.70(1H, d. d, J=4.8Hz, J=9Hz), 6.85(1H, s), 6.90(1H, s), 7.15~7.32(26H, b.s)

実施例12

7－〔2－(2－アミノチアゾール－4－イル)－2－アセチルオキシイミノアセトアミド〕－3－メチルチオ－3－セフエム－4－カルボン酸トリフロロ酢酸塩(シン異性体)：

7－〔2－(2－トリチルアミノチアゾール－4－イル)－2－アセチルオキシイミノアセトアミド〕－3－メチルチオ－3－セフエム－4－カルボン酸ジフエニルメチルエステル150mgをアニソール0.2ml中に氷冷下に加え溶解する。同温度で更にトリフロロ酢酸2mlを加え、氷冷下1時間撹拌する。

トリフロロ酢酸を減圧下20℃で濃縮し、残渣にイソプロピルエーテルを加え粉末化する。イソプロピルエーテル、エーテルで十分洗浄後、遠心分離機で分離する。減圧下乾燥し目的物55mgを得る。

IR(ヌジョール)；1770cm^{-1}

NMR(80 MHz, δ値, PPM, DMSO-d_6)；

2.16(3H, s), 2.32(3H, s), 3.75(2H, s), 5.12(1H, d, J=4.8Hz), 5.68(1H, d.d, J=4.8Hz, J=7.5Hz), 7.10(1H, s), 9.78(1H, d, J=7.5Hz)

実施例12と同様に対応する保護された3－セフエムセファロスポリン化合物の保護基をトリフロロ酢酸により除去し、次の実施例13～16の化合物を得た。

実施例13

7－〔2－(2－アミノチアゾール－4－イル)－2－プロピオノイルオキシイミノアセトアミド〕－3－メチルチオ－3－セフエム－4－カルボン酸トリフロロ酢酸塩(シン異性体)：

IR(ヌジョール)；1760cm^{-1}

NMR(80 MHz, δ値, PPM, DMSO-d_6)；

1.25(3H, t, J=8Hz), 2.26(3H, s), 2.50(2H, q, J=8Hz), 5.05(1H, d, J=5.0Hz), 5.70(1H, d.d, J=5.0Hz, J=8Hz), 7.05(1H, s), 9.80(1H, d, J=8Hz)

実施例14

7－〔2－(2－アミノチアゾール－4－イル)－2－イソブチリルオキシイミノアセトアミド〕－3－メチルチオ－3－セフエム－4－カルボン酸トリフロロ酢酸塩(シン異性体)：

IR(ヌジョール)；1760cm^{-1}

NMR(80 MHz, δ値, PPM, DMSO-d_6)；

1.15(6H, d, J=7.5Hz), 2.3(3H, s), 2.65(1H, m), 3.70(2H, b.s), 5.15(1H, d, J=5Hz), 5.70(1H, d.d, J=5Hz, J=8.2Hz), 7.05(1H, s), 9.85(1H, d, J=8.2Hz)

実施例15

7－〔2－(2－アミノチアゾール－4－イル)－2－ピバロイルオキシイミノアセトアミド〕－3－メチルチオ－3－セフエム－4－カルボン酸トリフロロ酢酸塩(シン異性体)：

IR(ヌジョール)；3300, 1770cm^{-1}

NMR(80 MHz, δ値, PPM, DMSO-d_6)；

1.20(9H, s), 2.30(3H, s), 3.75(2H, b.s), 5.15(1H, d, J=5Hz), 5.70(1H, d.d, J=5Hz, J=9Hz), 7.05(1H, s), 9.85(1H, d, J=9Hz)

実施例16

7－〔2－(2－アミノチアゾール－4－イル)－2－ピバロイルオキシイミノアセトアミド〕－3－エチルチオ－3－セフエム－4－カルボン酸トリフロロ酢酸塩(シン異性体)：

IR(ヌジョール)；1760cm^{-1}

NMR(80 MHz, δ値, PPM, DMSO-d_6)；

1.20(3H, t, J=8Hz), 1.25(9H, s), 2.70(2H, q, J=8Hz), 3.70(2H, b.s), 5.15(1H, d, J=5Hz), 5.72(1H, d.d, J=5Hz, J=8Hz), 7.1(1H, s), 9.80(1H, d, J=8Hz)

実施例17

7－〔2－(2－トリチルアミノチアゾール－4－イル)－2－アセチルオキシイミノアセトアミド〕－3－メチルチオ－3－セフエム－4－カルボン酸ピバロイルオキシメチルエステル(シン異性体)：

2－(2－トリチルアミノチアゾール－4－イル)－2－アセチルオキシイミノ酢酸(シン異性体)120mg及び7－アミノ－3－メチルチオ－3－セフエム－4－カルボン酸ピバロイルオキシ

メチルエステル９０㎎を乾燥塩化メチレン１０㎖に溶解し、これに１－ヒドロキシベンズトリアゾール３３㎎を加える。次いで氷冷下ジシクロヘキシカルボジイミド５０㎎を含む塩化メチレン１㎖を加える。５℃で終夜撹拌し不溶物を沪取し2.5％ HCℓ、水で順次洗浄する。乾燥後、減圧下濃縮乾固したのちシリカゲルクロマトに付し精製する。目的物１３０㎎を得る。

IR(ヌジョール)；3300, 1770, 1740～1710 cm^{-1}

NMR(80 MHz, δ値, PPM, $CDCℓ_3$)；

1.20(9H, s), 2.15(3H, s), 2.3(3H, s), 3.55(2H, b.s), 5.05(1H, d, J=4.8Hz), 5.15～5.35(3H, m), 6.85(1H, s), 6.95(1H, d, J=8Hz), 7.15～7.35(16H, m)

実施例１８

7－〔2－(2－トリチルアミノチアゾール－4－イル)－2－ピバロイルオキシイミノアセトアミド〕－3－メチルチオ－3－セフエム－4－カルボン酸ピバロイルオキシメチルエステル：

実施例１７と同様にして対応する３－セフエム化合物より標記化合物を得た。

NMR(80 MHz, δ値, PPM, $CDCℓ_3$)；

1.25(9H, s), 1.30(9H, s), 2.35(3H, s), 3.55(2H, b.d), 5.10(1H, d, J=5Hz), 5.60～5.95(3H, m), 6.85(1H, d, J=8Hz), 6.95(1H, s), 7.20～7.35(16H, m)

実施例１９

7－〔2－(2－アミノチアゾール－4－イル)－2－アセチルオキシイミノアセトアミド〕－3－メチルチオ－3－セフエム－4－カルボン酸ピバロイルオキシメチルエステル(シン異性体)：

7－〔2－(2－トリチルアミノチアゾール－4－イル)－2－アセチルオキシイミノアセトアミド〕－3－メチルチオ－3－セフエム－4－カルボン酸ピバロイルオキシメチルエステル(シン異性体)１００㎎をアニソール0.1㎖中に加え氷冷する。次いでトリフロロ酢酸１㎖加え、同温度で１時間撹拌し減圧下濃縮する。イソプロピルエーテルを加え粉末化し十分にイソプロピルエーテル、エーテルで順次洗浄する。粉末を酢酸エチル１０㎖に溶解し、氷冷下５％重炭酸ナトリウム水溶液で pH ＝ 7.0 に調整する。有機層を水洗後、硫酸マグネシウムで乾燥する。濃縮乾固し目的物３８㎎を得る。

IR(ヌジョール)；1760 cm^{-1}

NMR(80 MHz, δ値, PPM, $CDCℓ_3$)；

1.25(9H, s), 2.20(3H, s), 2.35(3H, s), 3.60(2H, b.s), 5.10(1H, d, J=5Hz), 5.70～5.95(3H, m), 6.90(1H, s), 8.25(1H, d, J=8Hz)

実施例２０

7－〔2－(2－アミノチアゾール－4－イル)－2－ピバロイルオキシイミノアセトアミド〕－3－メチルチオ－3－セフエム－4－カルボン酸ピバロイルオキシメチルエステル(シン異性体)：

実施例１９と同様にして標記化合物を得た。

NMR(80 MHz, δ値, PPM, $CDCℓ_3$)；

1.25(9H, s), 1.30(9H, s), 2.35(3H, s), 3.65(2H, b.s), 5.10(1H, d, J=5Hz), 5.70～5.95(3H, m), 6.95(1H, s), 7.60(1H, d, J=8Hz)

以　上

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弁理士　高野登志雄

弁理士　小野信夫

手 続 補 正 書（自発）

昭和 58 年 10 月 18 日

特許庁長官　若杉和夫　殿

1. 事件の表示
　昭和 58 年　特　許　願第 57 適 65 号

2. 発明の名称
　新規セファエム化合物

3. 補正をする者
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5. 補正命令の日付
　自　発

6. 補正の対象
　明細書の「発明の詳細な説明」の欄

7. 補正の内容
(1) 明細書中、第4頁第10行、
「で表わされる化合物を脱保護基として---
----」とあるを、
「で表わされる化合物の R_1^a の脱保護反応に付
して-------」と訂正する。
(2) 同、第7頁第9行、
「オキシムイミノ基」とあるを、
「オキシイミノ基」と訂正する。
(3) 同、同第12行、
「還元的に」とあるを、削除する。